FORMULATION AND EVALUATION OF MOUTH DISSOLVING FILM OF PERINDOPRIL BY USING NATURAL POLYMERS

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Submitted by
M.GUNA SUNDARI
REGISTRATION No.261410158

Under the guidance of
Dr. M. GOPAL RAO, M.Pharm., Ph.D.
Department of Pharmaceutics

COLLEGE OF PHARMACY
SRI RAMAKRISHNA INSTITUTE OF PARAMEDICAL SCIENCES
COIMBATORE – 641044

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CERTIFICATE

This is to certify that the M.Pharm dissertation entitled **"Formulation and Evaluation of Mouth dissolving Film of Perindopril by using Natural polymers"** being submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai was carried out by **Reg**. **261410158** in the Department of Pharmaceutics, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, under my direct supervision, guidance and to my fullest satisfaction**.**

Dr. M. GOPAL RAO, M.Pharm, Ph.D.,
Vice Principal & HOD,
Department of Pharmaceutics,
College of Pharmacy,
S.R.I.P.M.S
Coimbatore -641 044.

Place: Coimbatore
Date:

CERTIFICATE

This is to certify that the M.Pharm dissertation entitled **" Formulation And Evaluation of Mouth dissolving Film of Perindopril by Using Natural polymers "** being submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai was carried out by **Reg. 261410158** in the Department of Pharmaceutics, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, under the direct supervision and guidance of **Dr. M. GOPAL RAO, M.Pharm., Ph.D.,** Professor, Department of Pharmaceutics, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore.

Dr. T.K. RAVI, M.Pharm, Ph.D., FAGE.
Principal,
College of Pharmacy,
S.R.I.P.M.S
Coimbatore - 641 044.

Place: Coimbatore
Date:

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LIST OF ABBREVIATIONS

IP	:	Indian pharmacopoeia
USP	:	United states pharmacopoeia
FT-IR	:	Fourier transform infrared spectrometer
UV	:	Ultra violet
mm	:	milli meter
ml	:	milli litre
µg	:	micro gram
PMDF	:	perindopril mouth dissolving film
SEM	:	scanning electron microscope
DSC	:	differential scanning calorimetry
API	:	active pharmaceutical ingredient
FDFS	:	fast dissolving films
FDO	:	fast dissolving oral film
S	:	seconds
mg	:	milligram

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INTRODUCTION

Fast Drug Delivery Systems are rapidly gaining interest in the pharmaceutical industry. These systems either dissolve or disintegrate generally within a minute without needing water or chewing. These systems offer superior clinical profiles with potentional oro mucosal absorption thus increasing the drug bioavailability with respect to oral administration. Recently thin films have been proposed which rapidly dissolves or disintegrates into buccal cavity. Mouth dissolving films are novel dosage forms that disintegrate or dissolve in the oral cavity. These are ultra thin postage stamp size with an active agent or pharmaceutical excipients. These dosage forms are placed on the tongue or any mucosal tissue. When wet with saliva, the films rapidly hydrates and adheres on to the site of application. It rapidly dissolves or disintegrates to release the medicine for mucosal absorption or with modification, allows for oral GIT absorption with quick dissolving properties.

An important benefit of these dosage forms is accurate dosing as compared to liquid dosage form, no water is needed and there is no fear of choking as compared to tablets and capsules. After disintegrating in the mouth, enhanced the clinical effect of drug through pre-gastric absorption from mouth pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. More recently, Fast-dissolving buccal film drug delivery systems have rapidly gained acceptance as an important new way of administering drugs. They are usually used for pharmaceutical and nutraceuticals products. It is the newest frontier in drug delivery technology that provides a very convenient means of taking medications and supplements. Fast dissolving films are also applicable when local action in the mouth is desirable such as local anesthetic for toothaches, oral ulcers, cold sores, or teething

Oral route is the most preferred route of administration for systemic effect. About 60% of all formulations are of solid dosage form. Tablet is the most preferred dosage form due to ease of transportation, manufacturing and more patient compliance. Generally pediatric geriatric and forbidden patients experience difficulties in swallowing the conventional tablet. To overcome this problem a novel formulation was developed .i.e. oral fast dissolving films **(Siddiquinehal et al., 2011)** .

FDF is prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity, delivering the drug to the systemic circulation via buccal mucosa**. (Mahajan AN et al.,2011)**. The fast dissolving drug delivery system are specially designed for the drugs which have extensive first pass metabolism and have low dose, for the enhancement of bioavailability**. (Suresh B 2006)**.

Special features of Mouth dissolving films (Suresh et al.,2006)

- Thin elegant film
- Available in various size and shape
- Unobstructive
- Excellent mucoadhesion
- Fast disintegration
- Rapid release

Advantages of fast dissolving films(Bhura et al.,2012)

- Convenient dosing.
- No water needed.
- No risk of chocking
- Taste masking.
- Enhanced stability.

- Improved patient compliance.
- The drug enters the systemic circulation with reduced hepatic first pass effect.
- Site specific and local action.
- Availability of large surface area that leads to rapid disintegration and dissolution within oral cavity.
- Dose accuracy in comparison to syrup**.**

Disadvantages

- High doses cannot be incorporated.
- Dose uniformity is a technical challenge
- Hygroscopic in nature
- Require special packaging for products
- Stability and safety

Development of Oral Solid Dosage Form:

Various stages of development of the of oral solid dosage formulation

Simple conventional oral solid dosage forms(tablets,capsules)

↓

Modified release tablets/capsules

↓

Fast dissolving tablets/capsules

↓

Wafer to recent fast dissolving oral film

Overview of Oral Mucosa:

The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the sub mucosa as the innermost layer. The epitheliumis similar to stratified squamous epithelia found in the rest of the body in that it has a mitotic ally active basal cell layer, advancing through a number of Differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium.

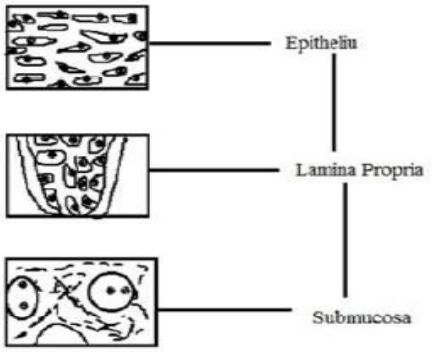


Figure 1: overview of oral mucosa

Ideal characteristics of suitable drug candidate (arya et al.,2010)

- The drug should have pleasant taste.
- The drug to be incorporated have low dose up to 40 mg.
- The drugs with smaller and moderate molecular weight are preferable.
- The drug should have good stability and solubility in water as well as in saliva.
- It should be partially unionized at the pH of oral cavity.
- It should have the ability to permeate oral mucosal tissue

Classifications of Fast Dissolve Technology

Fast-dissolve technologies can be divided in to three broad groups

- Lyophilized systems
- Compressed tablet-based systems
- Oral thin film

1. The lyophilized systems

This technology involves taking a suspension or solution of drug with other structural excipients, by using mould or blister pack, which forms tablet-shaped units. The units or tablets are then frozen and lyophilized in the pack or mould. The resulting units are of very high porosity, which allows rapid water or saliva penetration and very rapid disintegration.

2. Compressed tablet-based systems

The standard tablet technology by direct compression of excipients is used to produce this system. The tablet technologies have different levels of hardness and friability depending on the method of manufacture. The speed of disintegration for fast-dissolve tablets compared with a standard tablet is achieved by formulating it using water soluble excipients, super-disintegrant or effervescent components, to allow rapid penetration of water into the core of the tablet.

3. Oral thin film (Aggarwal et al., 2011)

It is also called as oral wafers. From the past few years the oral thin films are evolved in confection and oral care markets in the form of breath strips. These are novel and widely accepted form by consumers for delivering vitamins and personal care products. Such systems use a variety of hydrophilic polymers to produce a 50- 200 mm film**.**

Classification of Oral thin film

Following are the subtypes of oral fast dissolving films:

- Flash release.
- Mucoadhesive melt-away wafer.

METHOD OF PREPARATION OF MOUTH DISSOLVING FILMS (Mahajan A et al., 2011)

One or a combination of the following processes can be used to manufacture the Mouth Dissolving film:

- Solvent casting method
- Hot-melt extrusion
- Semisolid casting
- Solid dispersion extrusion
- Rolling

1. Solvent casting method

Water soluble ingredients are dis↓solved in water

↓

API and other agents are dissolved in suitable solvent

to form a clear viscous solution

↓

Both the solutions are mixed

↓

Degassed under vacuum

↓

Resulting solution is cast as a film

Advantage:

- ✓ Great uniformity of thickness and great clarity than extrusion
- ✓ Films have fine gloss & freedom from defect such a die liners
- ✓ Films have more flexibility & better physical properties

Disadvantage:

- ✓ Polymer must be soluble in volatile solvent or water
- ✓ The stable solution with reasonable minimum solid content

2. Hot melt extrustion

The drug is mixed with carriers in solid form

↓

Extruder having heaters melts the mixture

↓

Finally the melted mixture is shaped in films by the dies

Advantage:

- Fewer operation units
- Better content uniformity
- An anhydrous process

3. Semi solid casting

Solution of water soluble film forming polymer is prepared

↓

Resulting solution is added to a solution of acid insoluble polymer

↓

Appropriate amount of plasticizer is added to that gel mass is obtained

↓

Finally the gel is casted in to the films or ribbons using heat controlled drums

4. **Solid dispersion extrusion**

Drug is dissolved in a suitable liquid solvent

↓

The solution is incorporated in to melt of Polyethylene glycol
obtained below 70°c

↓

Finally the solid dispersions are shaped in to the films by means of dies

5. Rolling method

Prepare pre-mix with film forming polymer, polar solvent
And other additives except a drug

↓

Add premix to master batch feed tank

↓

Fed it via a first metering pumps and control valve to
Either or both of the 1 st and 2nd mixer

↓

Add required amount of drug to the desired mixer

↓

Blend the drug with master batch premix to give a uniform matrix

↓

Specific amount of uniform matrix is then fed to the pan
through 2nd metering pumps

↓

The film is finally forced on the substrate and carried
away via the support roller

↓

The wet film is then dried using controlled bottom drying

FORMULATION CONSIDERATION: (Aggarwal et al.,2011)

The area of drug loaded FDF should be between 1-20 cm^2. The drug can be loaded up to a single dose of 30mg.All excipient used in the fast dissolving film should be generally regarded as safe (GRAS-listed) and authorized for use in oral strip. Formulation considerations have been reported as important factors which affected mechanical properties of the films.

INGREDIENT AMOUNT

1. Drug(API) 5-30%
2. Water soluble polymer 45%
3. Plasticizer 0-20%
4. Saliva stimulating agent 2-6%
5. Surfactant Q.S.
6. Sweetening agent 3-6%
7. Flavours, colours, fillers Q.S.

Formulations of FDOFs having the characteristics such as taste masking, fast dissolution, physical appearance, mouth feel etc. All excipients used in the formulation of FDOF should be Generally Regarded as Safe (i.e. GRAS-listed) and should be approved for use in oral pharmaceutical dosage forms.

1. Drug Category

This technology has the potential for delivery of variety of APIs. However, there are some limitations like the size of the dosage form, drugs having high dose are difficult to be incorporated in films. Several classes of drugs can be formulated as fast dissolving films including antiulcer, antiasthamatics, antitussives, expectorants, antihistaminic and NSAID'S etc.

2. Film Forming Polymers

Water-soluble polymers are used as film formers as they provide rapid

disintegration, good Mouth feel and mechanical strength to the films. The robustness of the strip depends on the type of polymer and its amount in the formulations. Water-soluble polymeric film adheres to the bucosal mucosa and rapidly delivers medication into the systemic circulation. Various polymers are available for preparation of films of which pullulan, gelatin and hypromellose are most commonly used. Generally, 45%w/w of polymer should be present in the total weight of dry film.

Table 1: Film forming polymers

S.No.	Natural polymer	Synthetic polymer
1	Pullulan	Hydroxypropylmethyl cellulose
2	Starch gelatin	Polyvinyl pyrrolidone
3	Pectin	Polyvinyl alcohol
4	Sodium alginate	Carboxy methyl cellulose
5	Maltodextrin	Poly ethylene oxide
6	Polymerized rosin	Kollicoat
7	Lycoat NG 73	Hydroxypropyl cellulose
8	Xanthan	Hydroxyl ethyl cellulose

Ideal property of Film Forming Polymers:

- It should be non toxic and non irritant
- Polymer must be hydrophilic
- It should have excellent film forming capacity
- It should have good wetting and spread ability property
- Polymer should be readily available & should not be very expensive.
- Polymer should have low molecular weight.
- It should have sufficient shelf-life.

- Polymer must be tasteless, colorless.
- It should not cause any secondary infection in oral mucosa.
- It should exhibit adequate peel, shear and tensile strengths.

3. Plasticizers

It is a essential ingredient of the oral films. The selection of plasticizer depends upon its compatibility with the polymer and also the type of solvent employed in the casting of film. It improves the flexibility of the film and reduces the brittleness of the film. The strip properties of plasticizer are significantly improved by reducing the glass transition temperature of the polymer. They are used in the concentration of 1 - 20%w/w of dry polymer weight. Examples include: Glycerol, propylene glycol, Low molecular weight polyethylene glycols, Citrate derivatives like triacetin, acetyl citrate, phthalate derivatives like dimethyl, diethyl,dibutyl derivatives, Castor oil etc.

4. Sweetening agents

Sweeteners are the important part of the food products as well as pharmaceutical products. Incase of oral dosage form the sweet taste in formulation is more important especially for pediatric population. So, to improve the palatability of the mouth dissolving formulations natural sweeteners as well as artificial sweeteners are used. Following are the sweeteners which are suitable in FDF formulation:

(a) Water soluble natural sweetener: xylose, ribose, glucose, sucrose, maltose, stevioside etc.

(b) Water soluble artificial sweetener: sodium or calcium saccharin salts, cyclamate salts,acesulfame-k etc.

(c) Dipeptide based sweetener: aspartame

5. Saliva stimulating agent (Kaur Mandeep et al.,2013)

The saliva stimulating agents are used to increase the rate of production of saliva that is helpful in the faster dissolution of the film formulations. Generally acids which are used in the preparation of food can be utilized as salivary stimulants. Examples of salivary stimulants are as follows: citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid etc. Among these citric acid is most preferred saliva stimulating agent in the formulation**.**

6. Flavoring agents (Gavaskar Basani et al.,2010)

Preferably up to 10%w/w flavors are added in the OFDF formulations The acceptance of the oral disintegrating or dissolving formulation by an individual is largely depends on the initial flavor quality which is observed in first few seconds after the product has been consumed and the after taste of the formulation which lasts for at least about 10 min. The selection of flavor is dependent on the type of drug to be incorporated in the formulation. It was observed that age plays a significant role in the taste fondness. The geriatric population like mint or orange flavors while younger generation like flavors like fruit punch, raspberry etc. Flavoring agents can be selected from synthetic flavor oils, oleo resins, extract derived from various parts of the plants like leaves, fruits and flowers. Flavors can be used alone or in the combination. Peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg are examples of flavor oils while vanilla, cocoa, coffee, chocolate and citrus are fruity flavors. Apple, raspberry, cherry, pineapple are few examples of fruit essence type**.**

7. Colouring agents

Titanium dioxide or FD&C approved colouring agents are incorporated (not exceeding concentration levels of 1%w/w) in FDF formulation when some of the formulation ingredients or drugs are present in insoluble or suspension form.

EVALUATION OF FILM

1. Weigh variation of Films

Mouths dissolving oral films were weighed on analytical balance and average weight can be determined for each film. It is desirable that films should have nearly constant weight. It is useful to ensure that a film contains the proper amount of excipients and API.

2. Thickness of Films

By using micrometer screw gauge the thickness of the film was measured at five different places; an average of three values was calculated. This is essential to ascertain uniformity in the thickness of the film this is directly related to the accuracy of dose in the film.

3. Folding Endurance

Folding endurance is measured by manual repeated folding of film at same place till it broke.

The number of time the film is folded without breaking is known as the folding endurance value. **(Sumitha C.H et al.,2009)**

4. Tensile strength

Tensile strength is a maximum stress applied to a point at which the strip specimen breaks. It is calculated by applied load at rupture divided by the cross sectional area of the strip as given in the following equation:

Tensile strength = Load at failure × 100/film thickness × film width

5. Percent Elongation

When stress is applied to a film sample it stretches and this is referred as strain. Strain is basically the deformation of film divided by original dimension of the sample. Generally elongation of film increases as the plasticizer content

increases.

% Elongation = Increase in length× 100/ Initial length of film

6. Drug content uniformity

This is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia. Content uniformity is determined by estimating the API content in individual strip. Limit of content uniformity is 85-115%.

7. Surface pH

The film to be tested was placed in a Petri dish and was moistened with 0.5 ml of distilled water and kept for 30 s. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1 min. The average of three determinations for each formulation was done. **(Nagaret al.,2001)**

8. *In vitro* disintegration test

Disintegration time is the time when an oral film starts breaking when brought in contact with water or saliva. For a fast dissolving film, the time of disintegration should be in range of 5-30s. United State Pharmacopoeia (USP) disintegration apparatus can be used to study Disintegration time. In another method, the disintegration time can be visually determined by dipping the film in 25 ml water in a beaker. The beaker should be shaken gently and the time was noted when the film starts to breaks or disintegrates. **(Vishwkarma et al.,2001)**

9. Dissolution test

Dissolution testing can be performed using the standard basket or paddle apparatus described in any of the pharmacopoeia. The dissolution medium will essentially be selected as per the sink conditions and highest dose of the API.

Many times the dissolution test can be difficult due to tendency of the strip to float onto the dissolution medium when the paddle apparatus is employed**.** **(Dixit RP et al., 2009)**

10. Stability Testing

Stability measurement is done by storing the of oral strip were stored under controlled conditions of 25ºC/60% RH as well as 40°C/75% over a period of 12 months in stability chamber according to the ICH guideline. During storage period various evaluating parameter like thickness, morphological properties, tensile strength, water content and dissolution behavior are checked.

LITERATURE REVIEW

- Sandeep Saini et al.,(2011) formulated Fast dissolving film of levocetrizine dihydrochloride were prepared by solvent casting method by using Maltodextrin & HPMC E15 as the main film forming polymers. To decrease the disintegration time, concentration of maltodextrin & HPMC E15 were optimized be using 22 factorial design. Disintegration time, drug release pattern, mouth dissolving time and content uniformity were also evaluated. Compatibility between drug and recipients were studied by means of DSC analysis. Batch F1 was found to be the optimized batch as its disintegration was completed within the minimum time as compared to all other batches. The formulation (F1) was also showing sufficient drug release after 5 min. All the 6 formulation was showing approximately 90% drug release after 5min.

- Mital s panchal et al., (2012)Fast dissolving films of Ropinirole Hydrochloride were prepared by using polymers such as pullulan and PEG 400 as plasticizer, by a solvent casting method. The formulated mouth dissolving films were evaluated for physical characteristics such as uniformity of weight, thickness, folding endurance, drug content uniformity, surface pH, percentage elongation, and tensile strength, and gave satisfactory results. The formulations were subjected to disintegration, *In-vitro* drug release tests and stability study. The FTIR and DSC studies revealed that no physicochemical interaction between excipients and drug. A marked increase in the % drug release was exhibited by mouth dissolving films of Ropinirole Hydrochloride containing pullulan as a polymer at 60 sec., when compared to other polymers films. Mouth dissolving film of Ropinirole Hydrochloride containing pullulan as polymer showed 99.48 ± 0.18 % drug release at 60 sec.

- Mano Nagar et al.,(2012) formulated and evaluated matrix type mouth dissolving films of Aripiprazole, prepared by solvent evaporation technique using Hydroxy propyl Methyl Cellulose (HPMC) - 3 cps. The formulated films were evaluated for their physiochemical parameters like mouth dissolving time, surface pH, thickness & weight of the films, PMA, PML, folding endurance, taste, drug content, stability and *in vitro* bioequivalence. *In vitro* release studies were also performed in solutions of different pH. The mouth dissolving film was found to be bioequivalent to the conventional solid dosage form of Aripiprazole.

- Komagiri Sasi Deepthi et al., (2012) formulated atenolol fast dissolving films were formulated using film forming polymer like Hydroxy propyl methylcellulose (HPMC E5)(F1 – F8) and tween 80 is added to the formulation from F5 – F8 by solvent casting technique with the help of Polyethylene glycol (PEG 400) as a plasticizer and glycerine as a sweetening agent. FT-IR analysis was performed to study the interaction between the drug and polymer .The films were evaluated for weight variation, surface pH, folding endurance, drug content, dissolving time, disintegration time*, in-vitro* dissolution studies. Based on the evaluation parameters F4 containing Drug: Polymer (1:4) ratio showed optimum performance and marked increase in releasing of drug 92.34%, though F8 formulation has maximum drug release as it has less tensile strength. It can be concluded in the study that mouth dissolving film can be potential novel drug dosage form for poorly water soluble drugs.

- Buchi N Nalluri et al., (2013) formulating mouth dissolving films (MDFs) of the anti-asthmatic drug, Salbutamol Sulfate (SAL) to enhance convenience and compliance to the elderly and pediatric patients for better therapeutic efficacy. Film former, Hydroxy propyl Methylcellulose (HPMC) of different viscosity grades along with film modifier/solubilizing agents, polyvinyl pyrrolidone K30 (PVP K30) and sodium lauryl sulphate (SLS) were used to formulate MDFs. The MDFs were prepared by wet film applicator technique and were evaluated for

in vitro dissolution characteristics*, in vitro* disintegration time, and their physico-mechanical properties. MDFs with 13% (w/w) of HPMC E5 gave better dissolution properties when compared to HPMC E15.MDFs with 0.04% (w/w) of SLS gave superior dissolution properties when compared to MDFs without SLS. MDFs with 0.04% (w/w) PVP did not peel off from glass plate and hence were excluded from study.

- Sumedha Bansal et al., (2013) formulated a fast dissolving film of Losartan potassium films of were prepared by solvent casting method using polymers such as PVA and Maltodextrin in different ratios. Propylene glycol was used as a plasticizer. Films were subjected to physicochemical characterization such as thickness, weight uniformity, folding endurance, drug content, surface pH study, *in vitro* drug release, *ex vivo* permeation study and stability studies. The *in vitro* drug release in optimized formulation F8 was found to be 78.62 % in 4 min. The optimized formulation F8 also showed satisfactory pH, drug content (97.12%),), *ex vivo* permeation (89.42%), effective *in vitro* drug release (98.99% in 10min), disintegration time of 24 seconds and satisfactory stability.

- Buchi N. Nalluri et al.,(2013) formulating mouth dissolving films (MDFs) Sumatriptan Succinate (SUM) Film former, Hydroxy Propyl Methyl Cellulose along with film modifier/solubilizing agents, Polyvinyl pyrrolidone K30 (PVP K30) and Sodium Lauryl Sulphate (SLS) were used to formulate MDFs. The MDFs were prepared by wet film applicator technique and were evaluated for *in-vitro* dissolution characteristics, *in vitro* disintegration time, and their physico-mechanical properties. MDFs with 13% (w/w) of HPMC E5 gave better dissolution properties when compared to HPMC E15. MDFs with PVP K30and SLS gave superior dissolution properties when compared to MDFs without PVP K30 and SLS. The dissolution properties of MDFs with PVP K30 were superior when compared to MDFs with SLS.
- H.D. Karen et al.,(2013) developed Loratadine mouth dissolving films using HPMC E15 LV PREMIUM as film forming polymer, glycerin as a

plasticizer and tween 80 as a surfactant. The strips were evaluated for thickness, tensile strength, % elongation, disintegration time and *in vitro* drug release. A trial and error approach was used in present study for optimization. Oral strip containing HPMC E15 LV PREMIUM (190mg), tween 80 (15% of polymer) and glycerin (20% of polymer) has given the maximum *in vitro* drug release and imparts good transparency. A satisfactory result in the strip was exhibited in the way of *in vitro* release that came in 20 minutes. The drug excipients compatibility study showed that there were no interaction between drug and excipients. Stability study of the optimized formulation showed that the strips were stable at accelerated environmental conditions.

- K.M.Mageshwari et al..,(2014) formulated mouth dissolving films (MDFs) of Amlodipine Besylate(AMLO) using Film formers like hydroxy propyl methyl cellulose (HPMC) and methyl cellulose (MC) along with film modifiers like poly vinyl pyrrolidone K30(PVP K30), and sodium lauryl sulphate (SLS) as solubilizing agents were evaluated. The prepared MDFs were evaluated for *in vitro* dissolution characteristics, *in vitro* disintegration time, and their physico mechanical properties. All the prepared MDFs showed good mechanical properties like tensile strength, folding endurance, and % elongation. MDFs were evaluated by means of FTIR, SEM, and X-RD studies. MDFs with 7.5% (w/w) of HPMC E3 gave better dissolution properties when compared to HPMC E5, HPMC E15, and MC. Release kinetics data reveals diffusion is the release mechanism.

- Ravi Kumar K and Mercy Sulochana M (2014)formulated Lercanidipine hydrochloride fast dissolving films using polymers like HPMC E15, PVA as polymers and sodium starch glycolate, crospovidone as superdisintegrants by solvent casting method. Formulation HF2 with HPMC E15 and crospovidone is considered as the optimized formulation as it showed faster disintegration rate

(28sec), maximum i*n vitro* drug release i.e., 98.84% within 10mins. No significant changes were observed during stability studies for the optimized formulation. It was concluded that Lercanidipine hydrochloride fast dissolving oral films can be formulated as a potentially useful tool for an effective treatment of hypertension and management of angina pectoris with improved bioavailability, rapid onset of action and with increased patient compliance.

- Vidhi Desai, Nihar Shah (2014) formulated mouth dissolving films of Olmesartan Medoxomil, prepared by solvent casting technique. Film made up of different polymers but combination of HPMC E15 and PVA was optimized as final formulation. The prepared films were evaluated for organoleptic evaluations, film weight, thickness, folding endurance, tensile strength, drug content uniformity of films, surface PH disintegration time and in-vitro dissolution studies.

- Kamalesh upreti et al., (2014) formulated mouth dissolving films of paracetamol were prepared by solvent casting method, using polymer like (hydroxy propyl methyl cellulose) and plasticizer (glycerol) concentrations. Sweetening and flavoring agents were also added to make the formulation palatable. The films were evaluated for thickness, folding endurance, weight variation, disintegration time, dissolution time and drug content. Thickness of the films was approximately 2 mm. The strips disintegrated completely within 4 minutes. In-vitro dissolution studies were carried out in distilled water as well as in simulated salivary fluid (pH 6.8).The optimized formulation showed 92% drug release within 30 min. The prepared strips seem to be an attractive alternative to conventional marketed formulations.

- Ambikar R B et al.,(2014) Formulated herbal oral dissolving films contain herbal plants extract and powders of Ocimum tenuiflorum (tulasi), Azadiracta indica (neem), Syzygium aromaticum (lavanga),Boerhaavia diffusa (punarnava),

Glycyrrhiza glabra (yastimadhu), Jasminum grandiflorum (jasmine),(triphala). These plants possess antiulcer, astringent, antimicrobial and anti-inflammatory activity. HPMC and ethyl cellulose for the formulation of the films suitable polymers and plasticizers are selected. The films were subjected to physical investigations such as uniformity of thickness, weight, drug content, folding endurance, tensile strength, surface pH. Also evaluation of the films is done by using parameter like disintegration time, % moisture absorption, % moisture loss, surface pH, swelling index etc. The obtained results for prepared herbal films indicate that was higher for those formulations containing higher percentage of HPMC.

- Pandya Ketul et al.,(2014) formulated fast dissolving film of Telmisartan was prepared using Pullulan as film forming polymer. To decreases the disintegration time microcrystalline cellulose was used as filler. All the films were evaluated for their Thickness, Folding endurance, Tensile strength, % elongation, Disintegration time, *In vitro* drug release, and Stability study. The formulation F9 shows higher drug content (93.9%), Less Disintegration Time (33sec), Tensile Strength and Folding endurance respectively 0.249 N/mm2 and 243. Film of batch F9 was disintegrated with 33 second, Releases 93.22% drug within 16 minutes during the in *vitro* dissolution test and there was no significant change is shown during stability study.

- Poonam A Padamwar et al.,(2015) formulated Bisoprolol Fumarate film were prepared by using polymers such as hydroxy propyl methyl cellulose (HPMC) and Maltodextrin, plasticizer such as PEG 400, by a solvent casting method. They were evaluated for physical characteristics such as thickness, uniformity of weight, folding endurance, drug content, surface ph, percentage elongation and tensile strength and give satisfactory results. The formulations were subjected to disintegration, in-vitro drug release test. The *in vitro* disintegration time of the optimized batch F4 was found to be 20 sec. The

optimized batch was found to be stable for 1 month underspecified stability conditions.

- D Nagendra Kumar et al., (2015) formulated metaprolol succinate fast dissolving films using polymers like HPMC E5 and HEC polymer by solvent casting method. The prepared films were evaluated for organoleptic evaluations, film weight, thickness, folding endurance, tensile strength, drug content uniformity of films, surface PH disintegration time and *in vitro* dissolution studies. the formulation F5 has disintegration time of 7 seconds and is more promising and showed drug release of 98% after 5 minutes; hence formulation F5 was selected as best formulation.

- P Bhatt M Patel (2015) formulated Rizatriptan benzoate mouth dissolving films using polymers like HPMC, PVA, PVP K30, Xanthan gum, Guar gum. Citric acid was used as a saliva stimulating agent and Propylene glycol as a plasticizer. The prepared oral films were evaluated for their physicochemical and mechanical parameters such as Physical appearance, surface pH, thickness uniformity, disintegration time, drug content uniformity, folding endurance, tensile strength, percentage elongation, *in-vitro* drug release. The polymer combination of HPMC E 15 & PVA was optimized. On applying factorial design to this combination, batch with polymer ratio of 1:7 (HPMC: PVA) was optimized. The formulation was found stable after 1 month.

- Vasavi Geedi et al.,(2015) formulated Fast Dissolving Oral Films of Zolmitriptan Films were prepared by solvent casting method using Natural Polymers Xanthan gum, Guar Gum, Sodium Alginate, Aloe vera Powder as the film forming polymer and PEG-400 as the plasticizer. Vanillin was used as taste masking agent in the formulation. The thickness, folding Endurance, disintegration time, % drug released and drug content were selected as dependent variables. The optimized formulation, F6 was found superior than remaining 7

batches. Among all the formulations, F6 has shown maximum drug release of 99.1±0.05% within 8 min and a very low disintegration time of 8.33±0.57sec due to super-disintegrant Sodium Starch Glycolate. Hence the films made of 2%w/v of Sodium Alginate and PEG-400 showed excellent film forming property with rapid drug release profile. FT-IR studies revealed that there was no physico-chemical interaction between polymer and drug. Stability studies revealed that optimized formulation was stable as the % drug release at the end of 3rd month was 99.1%.

- Smita V. Pawar, M. S. Junagade (2015) formulated Risperidone fast dissolving films were formulated by solvent-casting method containing HPMC E5 as polymer and Propylene glycol as plasticizer. All films prepared were smooth and elegant in appearance and showed no visible cracks; were uniform in thickness, weight and drug content. Formulation A2 is considered as the optimized formulation as it showed good % elongation (120%), good folding endurance (185), faster disintegration rate (13 sec.) and maximum *in vitro* drug release (93.57%) within 10 mins. No significant changes were observed during stability studies for the optimized formulation. It was concluded that Risperidone fast dissolving oral films can be formulated as a potentially useful tool for an effective treatment of Schizophrenia with improved bioavailability, rapid onset of action and with increased patient compliance.

- Safila Naveed et al.,(2015) analyzed method development of perindopril. It is an angiotensin-converting-enzyme inhibitor (ACE inhibitor). In this method measurement of absorbance at the wavelength of maximum absorptions of Perindopril using water as a solvent is done. The calibration curve was linear in concentration range of 12.5-200 µg/ml for Perindopril with correlation coefficient of 0.9991. The accuracy and precision of the method was determined and validated statically. The method showed good recovery with % RSD less than 2 and good reproducibility. Method was found to be rapid, specific, precise and

accurate. This method can be successfully applied for the routine analysis of perindopril Accuracy of proposed method was confirmed by performing accuracy studies which showed the accepted results. Precision of proposed method was confirmed by performing intraday and inter day precision. The method for the determination of perindopril was validated according to ICH guidelines.

- Anjum Pathan et al., (2016) formulated and evaluate the Fast dissolving Oral film of Promethazine hydrochloride. The films were prepared Hydroxy propyl methyl cellulose E15 as a film base synthetic polymer and PEG400 (Poly Ethylene Glycol 400) as a plasticizer by solvent casting method. SLS (Sodium Lauryl Sulfate) and MCC (Micro Crystalline Cellulose) used as a surfactant in different concentration. Sucrose used as a sweetening agent and strawberry as a flavoring agent. Films were found to be satisfactory when evaluated for thickness, weight uniformity, *in-vitro* drug release, folding endurance, drug content and disintegration time. The *in vitro* drug release in optimized formulation F2 was found to be 14.36% in 2 min. The optimized formulation F2 also showed satisfactory pH, drug content (97.41±0.54%), effective *in vitro* drug release (96.03±0.68% in 16 min), disintegration time of 09 seconds and satisfactory stability.

POLYMER PROFILE

XANTHAN GUM

Synonyms

Corn sugar gum; E415; Keltrol; merezan; polysaccharide B-1459; xanthan gum.

Functional category

Stabilizing agent; suspending agent; viscosity-increasing agent.

Typical properties

Acidity/alkalinity pH	:	6-8 for a 1% w/v aqueous solution
Melting point	:	270 °C
Heat of combustion	:	14.6 J g
Specific gravity	:	1.600 at 25°C
Viscosity	:	1200-1600mPa.

Solubility

Practically insoluble in ethanol and ether. Soluble cold or warm water.

Description

Xanthan gum occurs as a cream or white –colored, odorless, free-flowing, fine powder.

Stability and storage conditions

Xanthan gum is a stable material. Aqueous solutions are over a wide pH range (pH 3-12) and temperatures between 60°C. Xanthan gum solutions less than1% w/v concentration may be adversely affected by higher than ambient temperatures.

Application in pharmaceutical formulation or technology

Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics and food as a suspending and stabilizing agent. It is non-toxic, compatible with most other pharmaceutical ingredients and has good stability and viscosity properties over a wide pH and temperature range. Although primarily used as a suspending agent Xanthan gum has also been used to prepare sustained release matrix tablets. Similarly optimum synergistic effects are obtained with Xanthan gum.

Safety

Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics and food products and is generally regarded as nontoxic and nonirritant at the levels employed as a pharmaceutical excipient.

SODIUM ALGINATE

Synonyms

Algin; alginic acid; sodium salt; E401; kelcosol; keltone; manucol; manugel; pronova; satialgine-H8.

Molecular weight

1828

Functional category

Stabilizing agent ; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity-increasing agent.

Typical properties

pH : 7.2(for a 1% w/v aqueous solution)

Melting point : 20ºC.

Specific gravity : 1.26.

Viscosity : 20-400 mPa

Solubility

Practically insoluble in ethanol and ether. Also insoluble in other organic solvents and acid. Slowly soluble in water, forminga viscous colloidal solution.

Description

Sodium alginate occurs as an odorless and tasteless, white to pale yellowish-brown colored powder.

Applications in Pharmaceutical formulation or Technology

Sodiumalginate is used in a variety of oral and topical pharmaceutical formulations. In tablet formulation sodium alginate may be used as a both binder and disintegrant. It has also been used for preparation of sustained release oral formulations since it can delay the dissolution of a drug from tablets. In topical formulations sodium alginate is widely used as a thickening and suspending agent in variety of creams and gels and as a stabilizing agent for oil in water emulsion.

Safety

Sodium alginate is widely used in cosmetics, food products and pharmaceutical formulations. It is generally regarded as a non-toxic and non irritant material although excessive oral consumption may be harmful.

PECTIN

Synonyms

Cellulose, kaopectate

Functional category

Stabilizing agent; gelling agent; thickening agent

Typical properties

Acidity/alkalinity pH	:	3.2-4.5
Melting point	:	270 °C
Heat of combustion	:	14.6 J g
Specific gravity	:	1.600 at 25°C
Viscosity	:	1200-1600 mPa.

Solubility

Pectin is soluble in pure water, partially soluble in cold water. It is Insoluble in organic solvents and alcohol.

Description

Pectin occurs as a white, amorphous, odorless, free-flowing, fine powder.

Stability and storage conditions

Pectin is a stable material. Aqueous solutions are over a wide pH range (pH 3-12) and temperatures between 60°C. Xanthan gum solutions less than1% w/v concentration may be adversely affected by higher than ambient temperatures.

Application in pharmaceutical formulation or technology

Pectin is widely used in oral and topical pharmaceutical formulations, gelling agent, thickener, water binder and stabilizer. It is non-toxic, compatible with most other pharmaceutical ingredients and has good stability and viscosity properties over a wide pH and temperature range.

Safety

Pectin is widely used in oral and topical pharmaceutical formulations, cosmetics and food products and is generally regarded as nontoxic and nonirritant at the levels employed as a pharmaceutical excipient.

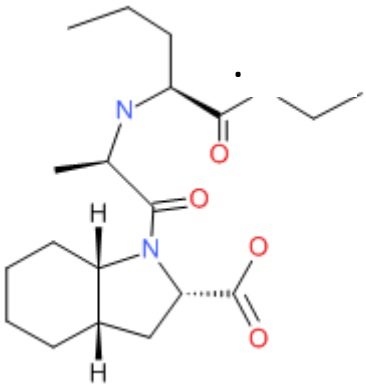
DRUG PROFILE

Synonyms : Perindopril

IUPAC Name : (2S,3AS.7as)-1-[(2S)-2-{[(2S)-1-ethoxy-1-oxopentan-2-yl]amino}propanoyl]octahydro-1H-indole-2-carboxylic perindoprilium.

Empirical Formula : $C_{19}H_{32}N_2O_5.C_4H_{11}N$

Structural Formula:



Molecular Weight : 368.468g/mol

Description : White to off white powder.

Solubility : Water, Methanol, Chloroform.

Melting point : 100-101° C.

Partition coefficient : Log P (n-octanol / water) is 3.018.

Storage : Store perindopril at room temperature, between 68-77° F. Store away from heat, light and moisture.

Category : ACE Inhibitor

Action and use : Perindopril is used in the treatment of hypertension and heart failure

Mode of action:

There are two isoforms of ACE: the somatic isoform, which exists as a glycoprotein comprised of a single polypeptide chain of 1277; and the testicular isoform, which has a lower molecular mass and is thought to play a role in sperm maturation and binding of sperm to the oviduct epithelium. Somatic ACE has two functionally active domains, N and C, which arise from tandem gene duplication. Although the two domains have high sequence similarity, they play distinct physiological roles. The C-domain is predominantly involved in blood pressure regulation while the N-domain plays a role in hematopoietic stem cell differentiation and proliferation. ACE inhibitors bind to and inhibit the activity of both domains, but have much greater affinity for and inhibitory activity against the C-domain.

Perindoprilat, the active metabolite of perindopril, competes with ATI for binding to ACE and inhibits and enzymatic proteolysis of ATI to ATII. Decreasing ATII levels in the body decreases blood pressure by inhibiting the pressor effects of ATII as described in the Pharmacology section above. Perindopril also causes an increase in plasma renin activity likely due to a loss of feedback inhibition mediated by ATII on the release of renin and/or stimulation of reflex mechanisms via baro receptors.

Pharmacokinetics:

Absorption and bioavailability:

Rapidly absorbed with peak plasma concentrations occurring approximately 1 hour after oral administration. Bioavailability is 65-75%. Following absorption, perindopril is hydrolyzed to Perindoprilat, which has an average bioavailability of 20%.

The rate and extent of absorption is unaffected by food. However, food decreases the extent of biotransformation to Perindoprilat and reduces its bioavailability by 35%.

Distribution:

Approximately 60% of circulating Perindopril is bound to plasma proteins, and only 10 to 20% of Perindoprilat is bound. Therefore, drug interactions mediated through effects on protein binding are not anticipated.

Biotransformation:

Extensively metabolized, with only 4-12% of the dose recovered in urine following oral administration. Six metabolites have been identified: Perindoprilat, perindopril glucuronide, Perindoprilat glucuronide, a perindopril lactams, and two Perindoprilat lactams. Only Perindoprilat is pharmacologically active. Perindoprilat and Perindoprilat glucuronide are the two main circulating metabolites.

Elimination:

Perindopril is extensively metabolized following oral administration, with only 4 to 12% of the dose recovered unchanged in the urine.

Dose:

Use in Uncomplicated Hypertensive Patients:

In patients with essential hypertension, the recommended initial dose is 4 mg once a day. The dose may be titrated, as needed to a maximum of 16 mg per day.

Use in Elderly Patients:

The recommended initial daily dosage of Perindopril for the elderly is4 mg daily, given in one or two divided doses.

Side Effects:

Heart

Slow heart rate, palpitations, heart block, abnormal heart rhythm, difficulty in breathing and chest pain.

Central Nervous System

Headache and dizziness.

Eye

Blurred vision.

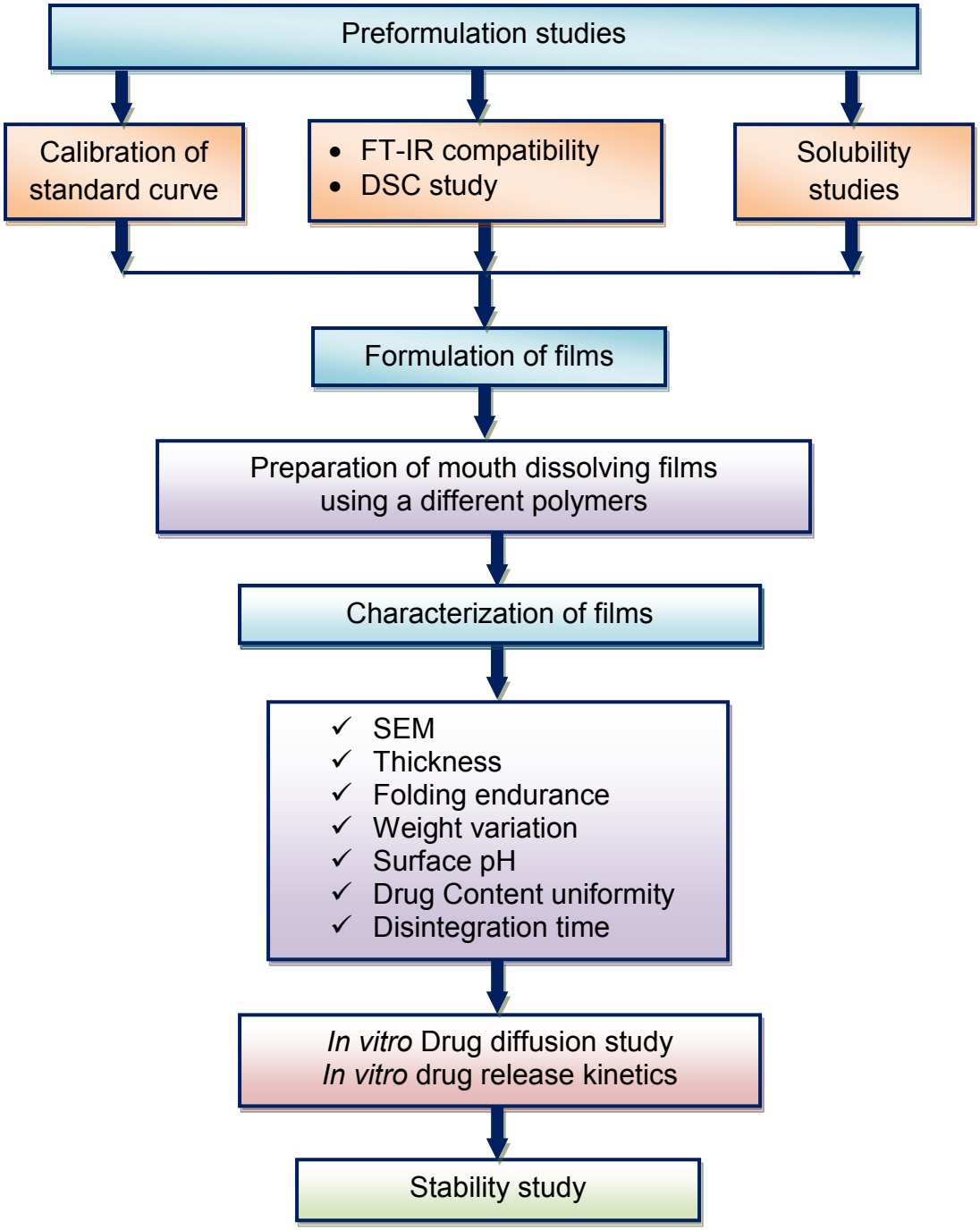
Gastrointestinal

Nausea, vomiting and stomach pain.

Musculoskeletal

Muscle cramps and muscle weakness.

PLAN OF WORK


Preformulation studies
Calibration of standard curve
FT-IR compatibility
DSC study
Solubility studies
Formulation of films
Preparation of mouth dissolving films using a different polymers
Characterization of films
✓ SEM
✓ Thickness
✓ Folding endurance
✓ Weight variation
✓ Surface pH
✓ Drug Content uniformity
✓ Disintegration time
In vitro Drug diffusion study
In vitro drug release kinetics
Stability study

MATERIALS AND EQUIPMENTS

MATERIALS USED

MATERIAL	SOURCE
Perindopril	Hetero Drugs Ltd, Hyderabad**.**
Xanthan gum	Loba Chemicals,Mumbai.
Sodium alginate	Ozone International,Mumbai.
Pectin	Himedia Laboratories, Mumbai.
Sodium starch glycolate	Loba chemical Pvt Ltd, Mumbai.
Poly ethylene glycol (400)	Qualigens Fine Chemicals,Mumbai.
Vanillin	Himedia Laboratories, Mumbai.
Sucrose	Sisco Research Laboratories, Mumbai.
Pottasium dihydrogen phosphate	Himedia Laboratories, Mumbai
Disodium hydrogen phosphate	Sd Fine Chemicals, Mumbai

EQUIPMENTS USED

EQUIPMENT	MODEL/COMPANY
DSC	Shimadzu corporation, japan.
Uv-visible spectrophotometer	Jasco V 530
FT-IR Spectrophotometer	Jasco-FTIR 4100
Digital balance	Shimadzu corporation japan
Dissolution test apparatus	Electro lab TDT 08L
pH tester	Eutech instruments
Disintegration tester	Campbell electronics, Bombay.
SEM	JSM 6390, Make – JEOL

EXPERIMENTAL METHODS

ESTIMATION OF PERINDOPRIL

The methods for estimation of perindopril reported include Ultra Violet (PanchumarthyRavisankar et al., 2015), High Performance Liquid Chromatography (Nagaraju et al., 2014), Reverse Phase High Performance Liquid Chromatography (Krishna Chaitanya Prasad et al., 2013), High Performance Thin Layer Chromatography (Santosh et al., 2014).

Method used for the estimation of perindopril in this present investigation

A uv spectrophotometric method based on the measurement of absorbance at 210 nm was used in the present study for the estimation of perindopril for the samples. Calibration curves were constructed for the perindopril in 20-100µg/ml.

Construction of calibration curve of perindopril by UV spectrophotometry

Preparation of pH 6.8 phosphate buffer (IP 2007 vol 1)

Dissolve 28.8g of disodium hydrogen phosphate and 11.45g of potassium dihydrogen phosphate in sufficient water to produce 1000 ml.

Calibration graphs preparation in Phosphate buffer pH 6.8

100 mg of pure drug perindopril was accurately weighed and transferred to 100 ml of volumetric flask. Drug was dissolved in phosphate buffer 6.8 and volume was made up to 100 ml. The concentration of drug was 1000 µg/ml.

Standard solution

100mg of perindopril was dissolved in a 100 ml of volumetric flask and this solution was made up to the mark with water.

Procedure for plotting calibration curve of pure drug

From the standard solution of perindopril was subsequently diluted with water to obtain a series of dilutions containing 20-100 µg/ml of perindopril in 1 ml solution. The absorbance of these solutions was measured at 221 nm UV spectrophotometer (JASCOV530) against corresponding blank. The concentration of perindopril and the corresponding absorbance values are given in table 5. The calibration curves for the estimation of perindopril were constructed by plotting linear best fit between concentration of perindopril and corresponding mean absorbance value are shown in figure 2.

IDENTIFICATION OF PERINDOPRIL

Perindopril was received as a gift sample from CTX Life Science Pvt. Ltd, India.

Fourier Transform Infrared (FT-IR) Spectroscopy

FT-IR spectrum of drug was recorded using a JASCO 4100. The diffuse reflectance technique was utilized in the mid IR 4000-400 cm^{-1} spectral region. The procedure consist of dispersing the sample in kbr (100mg) using a motor, triturating the materials into a fine powder bed into the holder using compression gauge. The pressure was around 5 tons for 5 min. The pellet was placed light path and the spectrum was recorded in duplicate, the characteristic peaks of the functional groups were interpreted.

UV Spectroscopy

An accurately weighed 10 mg of drug was dissolved in 10 ml water. From the primary stock solution 20 µg/ml of perindopril solution was prepared phosphate buffer solution. This solution was scanned between 200-400 nm.

PREPARATION OF PERINDOPRIL MOUTH DISSOLVING FILMS

Solvent casting method involves firstly the water soluble polymers are dissolved in water at 1,000 rpm and can be heated up to 60°C. All the other excipients like colors, flavoring agent, sweetening agent, etc., are dissolved separately. Then both the solutions obtained are mixed thoroughly stirring at 1,000 rpm. The obtained solution is incorporated with the API dissolved in suitable solvent. The entrapped air is removed by vacuum. The resulting solution is cast as a film and allowed to dry, which is then cut into pieces of the desired size. The formulation codes are given in the table4.

Table 2: Composition of fast dissolving films of perindopril using Xanthan gum (F1-F5)

INGREDIENTS	FORMULATION				
Formulation code	**F1**	**F2**	**F3**	**F4**	**F5**
Drug (mg)	20	20	20	20	20
Xanthan gum(mg)	100	150	200	250	300
Poly ethylene glycol 400(ml)	0.4	0.4	0.4	0.4	0.4
Sodium starch glycolate(mg)	10	10	10	10	10
Citric acid (mg)	5	5	5	5	5
Sucrose(mg)	5	5	5	5	5
Vanillin(mg)	5	5	5	5	5
Amaranth(mg)	qs	qs	qs	qs	qs
Water(ml)	8	8	8	8	8

Table 3: Composition of fast dissolving films of perindopril using sodium alginate (F6-F10)

INGREDIENTS	FORMULATION				
Formulation code	**F6**	**F7**	**F8**	**F9**	**F10**
Drug (mg)	20	20	20	20	20
Sodium alginate (mg)	100	150	200	250	300
Poly ethylene glycol 400(ml)	0.4	0.4	0.4	0.4	0.4
Sodium starch glycolate(mg)	10	10	10	10	10
Citric acid (mg)	5	5	5	5	5
Sucrose(mg)	5	5	5	5	5
Vanillin(mg)	5	5	5	5	5
Amaranth(mg)	qs	qs	qs	qs	qs
Water(ml)	8	8	8	8	8

Table 4: Composition of fast dissolving films of perindopril using pectin (F11-F15)

INGREDIENTS	FORMULATION				
Formulation code	**F11**	**F12**	**F13**	**F14**	**F15**
Drug (mg)	20	20	20	20	20
Pectin (mg)	100	150	200	250	300
poly ethylene glycol 400(ml)	0.4	0.4	0.4	0.4	0.4
Sodium starch glycolate(mg)	10	10	10	10	10
Citric acid (mg)	5	5	5	5	5
Sucrose(mg)	5	5	5	5	5
vanillin(mg)	5	5	5	5	5
Amaranth(mg)	qs	qs	qs	qs	qs
Water(ml)	8	8	8	8	8

DRUG-EXCIPIENTCOMPATIBILITY STUDIES

Before formulation of a drug substance into a dosage form, it is essential that it should be chemically and physically compatibility. Compatibility studies give the information needed to define the nature of the drug substance and provide a frame work for the drug combination with pharmaceutical excipients in the fabrication of a dosage form.

One of the requirements for the selection of suitable excipients or carrier for pharmaceutical formulation is its compatibility. Therefore in the present work, a study was carried out by using infrared spectrophotometer to find out if there is any possible chemical interaction between perindopril and excipients.

Weighed 3 mg of drug was mixed with 100 mg of potassium bromide (dried at 40-50˚c). The mixture was taken and compressed under 10-ton pressure in hydraulic press to form a transparent pellet. The pellet was scanned from 4000-400cm-1 in IR spectrophotometer.

The result was shown in Figure 3-9.

FT-IR peak matching

FT-IR spectra matching approach of the FT-IR data was employed for detection of chemical interaction between the drug and selected polymers. The chemical interaction between drug and polymer can be identified by changes in the peak (characteristic wave numbers). Physical mixture of drug, polymer and drug & polymer were prepared and mixed with suitable quantity of potassium bromide separately. About 100 mg of this sample was compressed to form a transparent pellet using a hydraulic press at 15 tons pressure. It was scanned from 4000-400/cm. FT-IR spectra of pure drug, polymer and drug formulation was compared to detect any appearance or disappearance of peaks.

Drug-Excipient Compatibility Studies by DSC:

DSC thermo grams of pure drug (perindopril) and its physical mixture with polymer (pectin) were carried out to investigate any possible interaction between the drug and the utilized polymer (Pectin).The selected heating rate is from 50°C to 300°C at an increase of 20°C per minute using Differential Scanning Calorimeter (Shimadzu corporation, Japan)

CHARACTERIZATION OF FILMS

Scanning electron microscope

The surface morphology of optimized formulation was studied using scanning electron microscopy. A scanning electron microscopic sample holder with a double sided taps and coated with a layer of gold of 150 $^{\circ}$A for 2 min using a sputter coater(JSM 6390, Make – JEOL) in a vaccum of 3×10^{-1}atm of organ gas. The samples were then examined using a scanning electron microscope (Gupta Dilip Kumar et al., 2014).

Weight variation

Mouths dissolving oral films were weighed on analytical balance and average weight can be determined for each film. It is desirable that films should have nearly constant weight. It is useful to ensure that a film contains the proper amount of excipients and API.

Thickness of Films

By using micrometer screw gauge the thickness of the film was measured at five different places; an average of three values was calculated. This is essential to ascertain uniformity in the thickness of the film this is directly related to the accuracy of dose in the film. (Swapnali V Bande et al.,2007)

Folding endurance

Folding endurance was determined by repeated folding of the strip at the same place till the strip breaks. The number of times the film was folded without breaking is computed as the folding endurance value. (Arya A., 2010)

Drug content uniformity

This is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia. Content uniformity is determined by estimating the API content in individual strip. Limit of content uniformity is 85-115%. (Sharma R et al., 2005)

Surface pH

The film to be tested was placed in a Petri dish and was moistened with 0.5 ml of distilled water and kept for 30 s. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1 min. The average of three determinations for each formulation was done. (Kumar GV et al.,2005)

***In vitro* disintegration test**

Disintegration time is the time when an oral film starts breaking when brought in contact with water or saliva. For a fast dissolving film, the time of disintegration should be in range of 5-30s. United State Pharmacopoeia (USP) disintegration apparatus was used to studydisintegration time. In another method, the disintegration time was visually determined by dipping the film in 25 ml water in a beaker. The beaker was shaken gently and the time was noted when the film starts to breaks or disintegrates. (Vishwkarma DK et al.,2011)

***In vitro* diffusion studies**

In vitro drug release studies were performed by using Franz diffusion cell with dialysis membrane. It consists of a donor compartment and a receptor compartment. The receptor compartment was filled with 20ml of phosphate buffer

solution as a diffusion medium. The prepared film was taken in the receptor compartment the medium was continuously stirred at 50 rpm using magnetic beads and the temperature was maintained at 37±1˚C. 1ml sample of receptor fluid was withdrawn at predetermined intervals and volume was replaced with same volume of 1ml phosphate buffer solution. The sample was analyzed spectrophotometrically at 210 nm using JASCO V 530uv spectrophotometer. The cumulative amount of drug permitted was calculated and plotted against time. (Rahul Nair et al.,2012).

***In vitro* drug release kinetics**

The order and mechanism of drug release kinetics of perindopril films was analyzed by the *invitro* diffusion study data by plotting the following kinetic models, (zero order, first order and Higuchi equations and release was determined by using Korsmeyer-Peppas equations.

Zero-Order Kinetics:

Cumulative amount of drug released was plotted against time.

$$C = K_0 t$$

Where K_0 is the zero-order rate constant expressed in units of concentration/time and *t* is the time in hours. A graph of concentration Vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axis. This kinetics describes concentration independent drug release from the formulations.

First order kinetics:

First order as log cumulative percentage of drug remaining vs time. This kinetics describes concentration dependent drug release from the formulations.

$$\text{Log } C = \text{Log } Co - kt / 2.303$$

Where C_0 is the initial concentration of drug, *k* is the first order constant, and *t* is the time.

Higuchi's Model:

Higuchi's model as cumulative percentage of drug released vs square root of time.

$$Q = Kt^{1/2}$$

Where *K* is the constant reflecting the design variables of the system and *t* is the time in hours. This model describes the release of drug on the basis of Fickian diffusion as a square root of time dependent process from swellable matrix.

Korsemeyer-Peppas Equations:

The mechanism of drug release, the first 60% of drug release were plotted in Korsemeyer et al's equation log cumulative percentage of drug released vs log time, and the exponent *n* was calculated through the slope of the straight line,

$$Mt / M\infty = Kt^{n}$$

Where Mt/M∞ is the fractional solute release, t is the release time, K is a kinetic constant. Characteristic of the drug/polymer system, and n is an exponent that characterizes the mechanism of release of tracers. For cylindrical matrix tablets, if the exponent n = 0.45, then the drug release mechanism is Fickian diffusion, and if 0.45 <*n* < 0.89, then it is non-Fickian or anomalous diffusion. An exponent value of 0.89 is indicative of Case-II Transport or typical zero-order release (Balaiah et al.,2012).

RESULTS AND DISCUSSION

ANALYTICAL METHOD TO DETERMINE PERINDOPRIL

Estimation of perindopril using UV Spectrophotometry

Perindopril was estimated using UV spectrophotometry measured at 210 nm using phosphate buffer (pH 6.8).

Table 5: Estimation of perindopril measured at 210 nm in phosphate buffer (pH 6.8) using uv spectrophotometry

S.No	Concentration (µg/ml)	Absorbance at 210nm
1	20	0.2045±0.0045
2	40	0.4021±0.0021
3	60	0.6125±0.0025
4	80	0.7923±0.052
5	100	1.0100±0.083

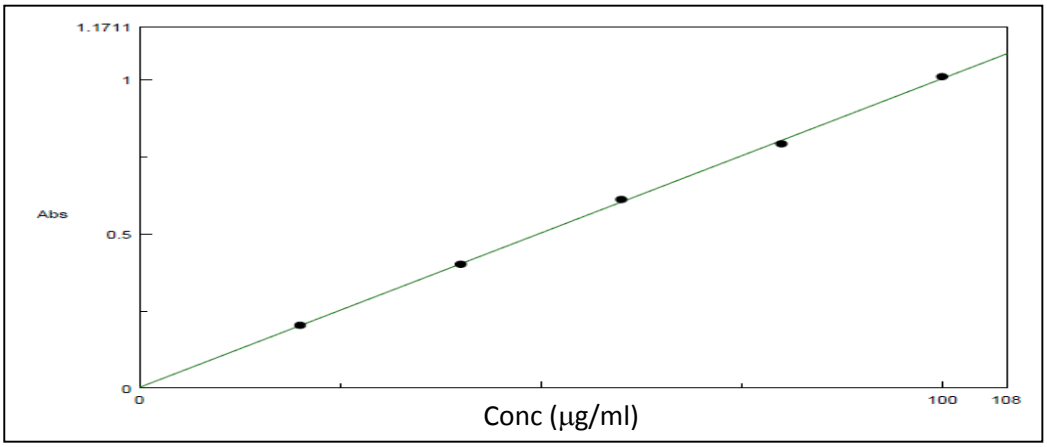


Figure 2: Estimation of perindopril measured at 210 nm in phosphate buffer (pH 6.8) using UV spectrophotometry

It was observed that the concentration range of 2-10µg /ml obeyed the Beer's Lambert's law. The correlation coefficient was found to be R = 0.998816.

COMPATIBILITY STUDIES

The compatibility study between drug and the carriers was carried out using FTIR spectrometer. The peak numbers of the drug exhibiting O-H, C-H, C-C, C=N stretching were observed and are depicted as below. (Skoog DA *et al*., 2007)

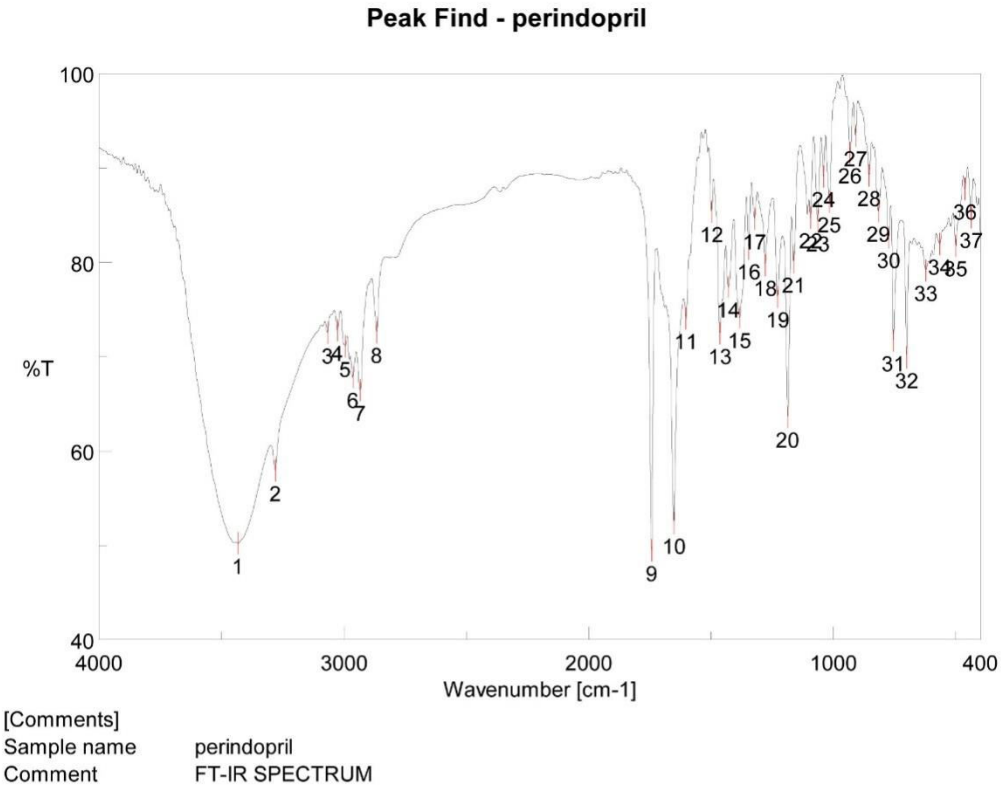


Figure 3: FTIR spectrum of perindopril

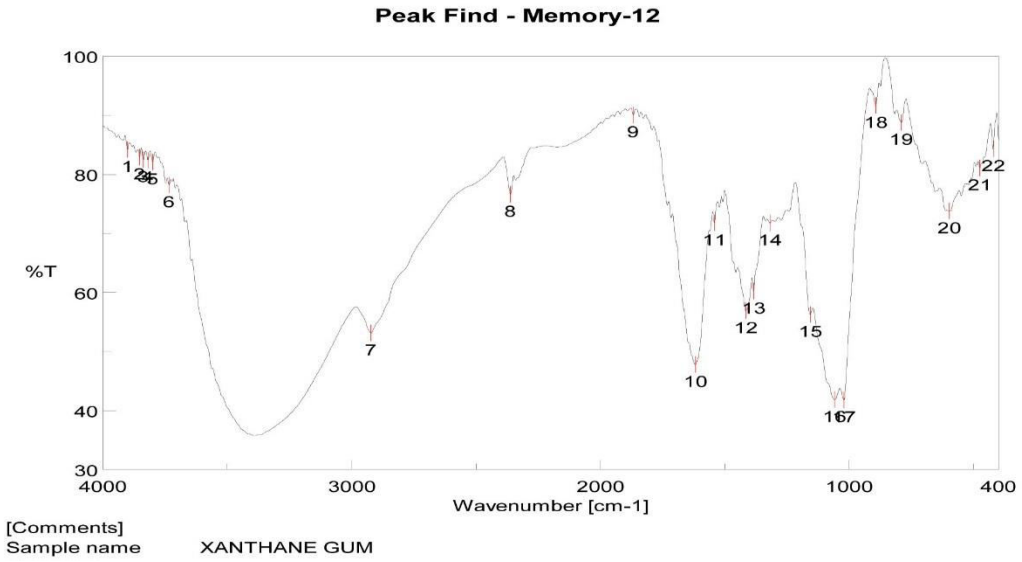


Figure 4: FTIR spectrum of Xanthan gum

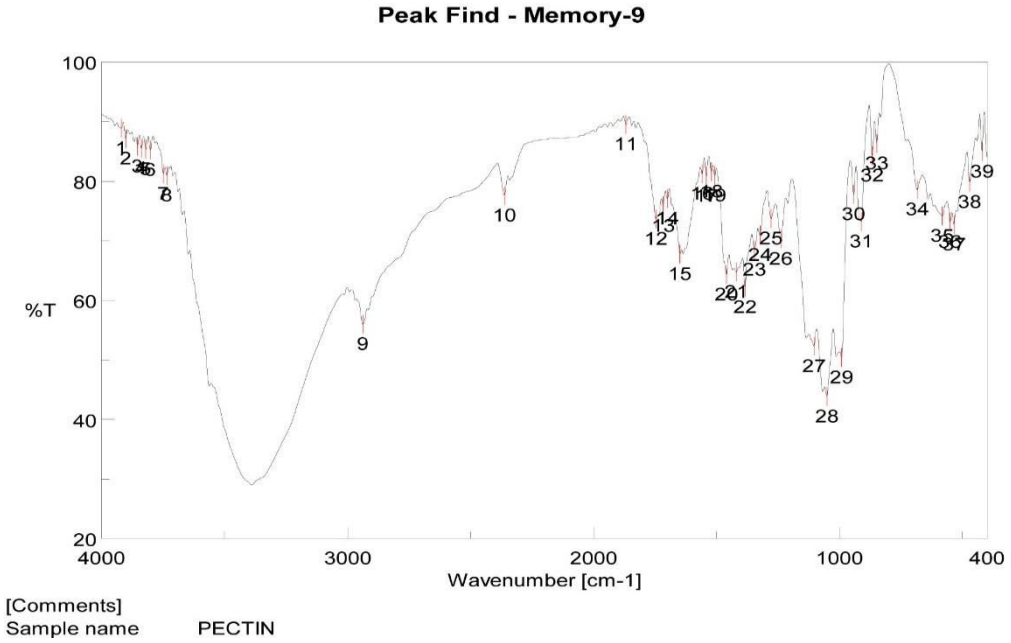


Figure 5: FTIR spectrum of Pectin

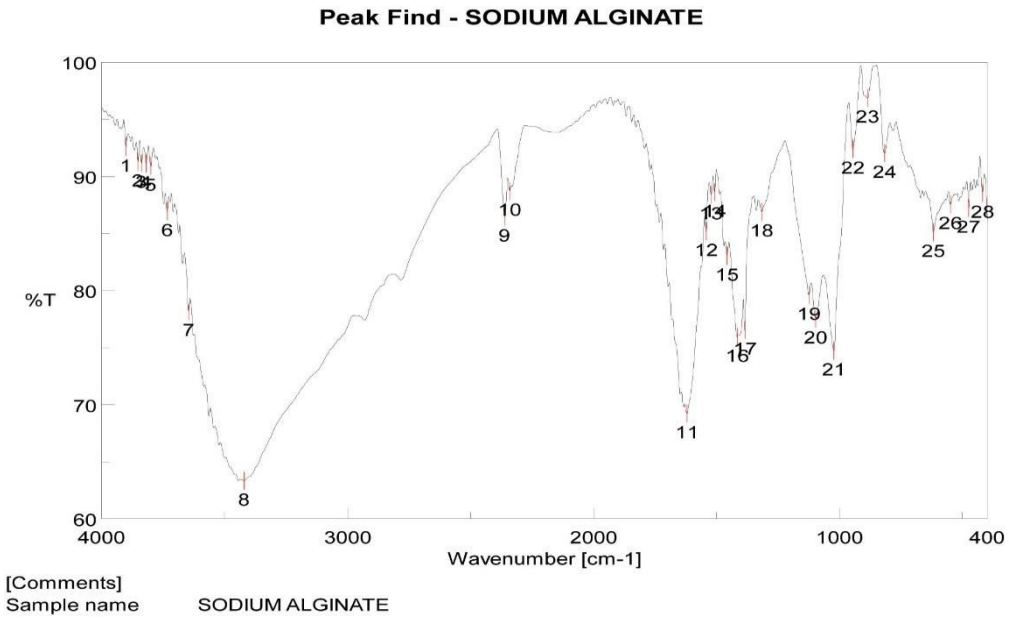


Figure 6: FTIR spectrum of sodium alginate

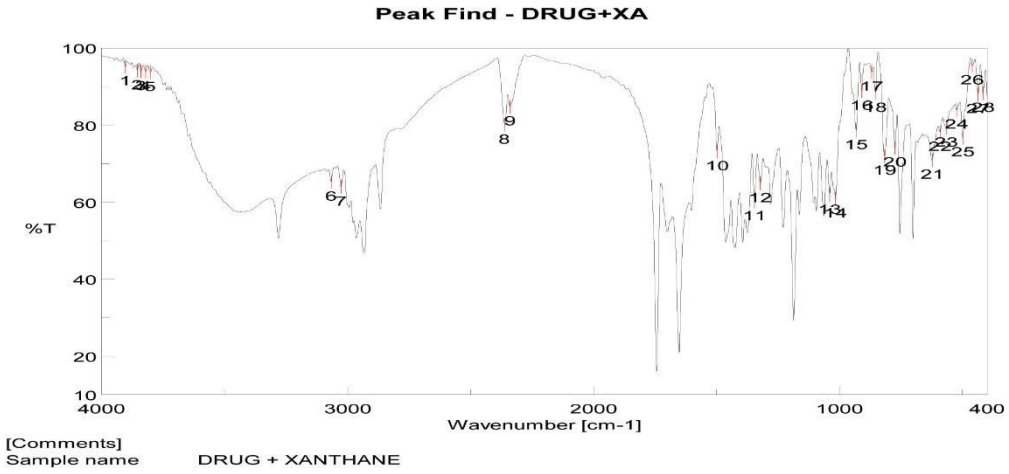


Figure 7: FTIR spectrum of perindopril with Xanthan gum

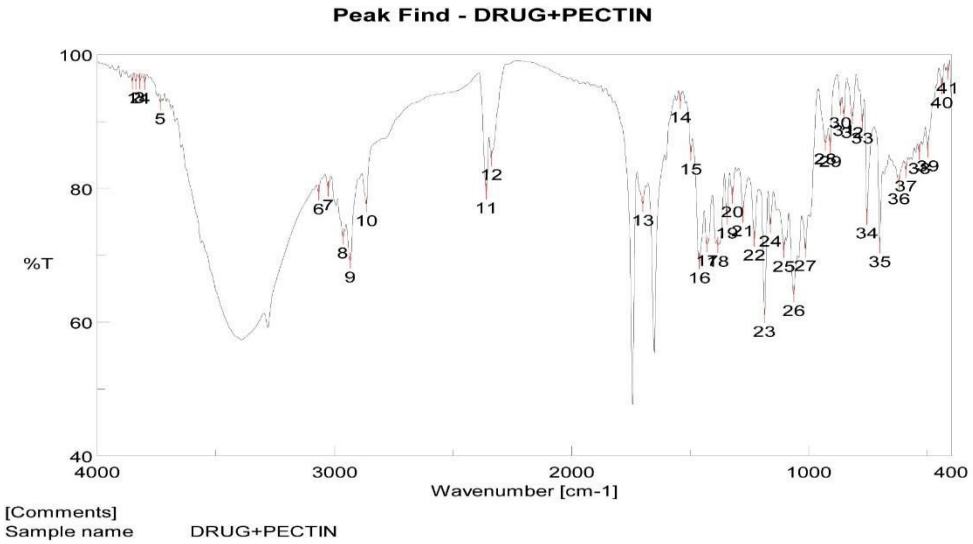


Figure 7: FTIR spectrum of perindopril with pectin

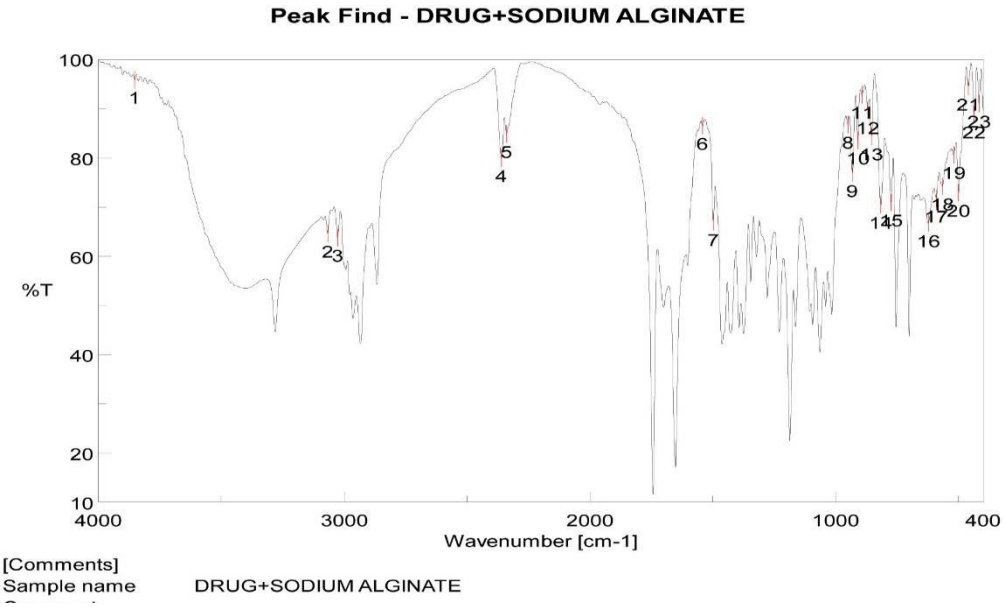


Figure 9: FTIR spectrum of perindopril with sodium alginate

Table 6: IR spectrum of perindopril and excipients

(sodium alginate, guar gum, pectin)(Skoog DA *et al*., 2007)

Functional group assignment	Standard wave number (cm^{-1})	Test wave number (cm^{-1}) of drug	Test wave number (cm^{-1}) of excipients		
			Xanthan gum	pectin	Sodium alginate
N-H stretching	3000-3600	3432.67	-	-	3420.14
CH stretching	2700-3300	2964.05	2922.59	2938.02	2922.5
N-H bending	1500-1700	-	1541.81	1541.81	1542.77
COOH stretching	1500-1760	1743.33	1618.95	1648.84	1620
Alkanes(bending)	1340-1470	1429.96	1415	1420	1420
C-N stretching	1180-1360	1186.97	1317.1	1317	1317.1
O-H bending	1200-1400	1228.43	1384.64	1345	1384
C-F stretching	1100-1250	1162.87	1157.0	1159.0	1159.0
N-H rocking	700-900	816.706	893.84	848.74	842.74
Mono sub benzene ring(rocking)	730-770	754.55	790.69	746.31	746.31
C-O stretching	1050-1300	1278.57	1058.73	1501	-

Table 7: IRspectrum of Perindopril with excipients

(Xanthan gum, sodium alginate, pectin) (Skoog DA *et al*., 2007)

Functional group assignment	Standard wave number (cm^{-1})	Test wave number (cm^{-1}) of drug	Test wave number (cm^{-1}) of excipients		
			Drug + Xanthan	Drug +SA	Drug+ pectin
N-H stretching	3000-3600	3432.67	3067.23	3067	3420.14
CH stretching	2700-3300	2964.05	3026.73	3026.73	2922.5
N-H bending	1500-1700	-	1498.42	1541.81	1542.77
COOH stretching	1500-1760	1743.33	1648.95	1648.84	1620
Alkanes(bending)	1340-1470	1429.96	1415	1420	1420
C-N stretching	1180-1360	1186.97	1321.1	1317	1317.1
O-H bending	1200-1400	1228.43	1346.64	1345	1384
C-F stretching	1100-1250	1162.87	1016.0	1159.0	1159.0
N-H rocking	700-900	816.706	815	848.74	842.74
Mono sub benzene ring(rocking)	730-770	754.55	750.69	746.31	746.31
C-O stretching	1050-1300	1278.57	1058.73	1501	-

The physical mixture of perindopril and excipients was subjected to FTIR to identify any interaction between them.

There was no appearance or disappearance of any characteristic peak of the drug, which confirms the absence of chemical interaction between drug and carrier.

Hence the excipients sodium alginate, xanthan gum, pectin which was observed to be compatible with perindopril was selected for further development of the formulation.

DRUG EXCIPIENT COMPATABILITY STUDY BY DSC:

A sharp exothermic peak was observed of the drug at 127.7°C, corresponding to its melting point of the drug.(126°C -128°C).

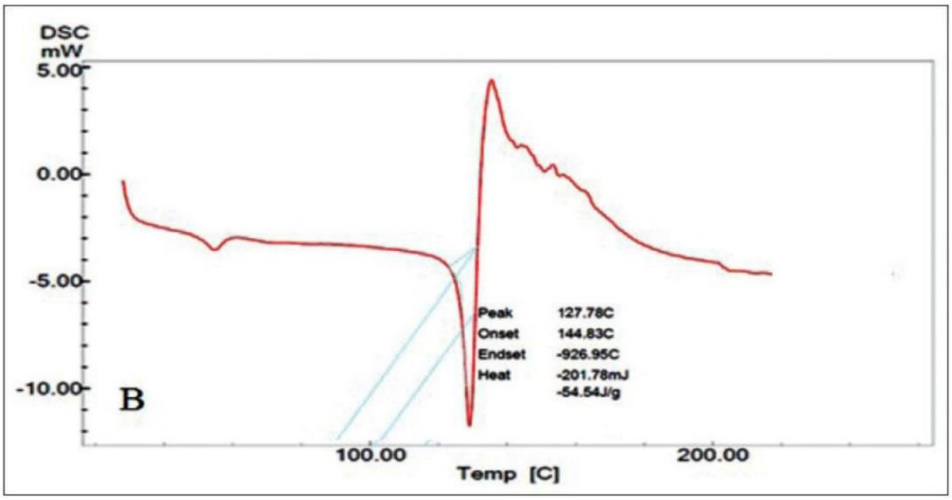


Figure 10: DSC thermo gram of F13 formulation

EVALUATION OF FILMS

Surface morphology

Sample of PMDF prepared by fracturing the films in liquid nitrogen, mounted on aluminum stubs, and sputter coated with platinum and surface morphology of PMDF was studied by scanning electron microscopy (SEM) with magnification of X5000 at 20kv. (JEOL 5400, Tokyo, Japan).

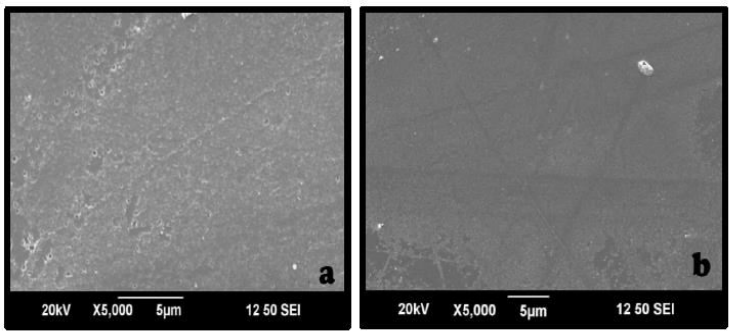


Figure 10: SEM of Mouth dissolving film (a) upper surface and (b) lower surface

EVALUATION OF FILMS

Thickness

The thickness of all formulations F1- F15 was found by using digital micrometer and the results were shown in the table.

Table 8: Determination of thickness for Different formulations of perindopril films (F1-F15)

Formulation	Thickness (µm)± SD
F1	95±5
F2	100±5
F3	102±2.5
F4	99±3.6
F5	99±1
F6	96.6±1.5
F7	97±2.5
F8	100±3.5
F9	97.6±2.5
F10	102±4
F11	103±2.6
F12	98±3.2
F13	99±2.6
F14	100±1.3
F15	95±2

The thickness of F1 to F15 was found to be 48-110µm. From the results obtained from the above formulations, all formulations showed thickness of films as 5-200µm and complies with the limit as per the previous value.

FOLDING ENDURANCE: (Kaur Mandeep etal., 2013)

Three films of each formulation were cut by using sharp blade. Folding endurance was determined by repeatedly folding a small strip of film at the same

place till it break. The number of times, the film could be folded at the same place without breaking gave the value of folding endurance. The mean values of three readings were calculated.

Table 9: Determination of folding endurance for Different formulations of perindopril films (F1-F15)

Formulation	Folding endurance
F1	50
F2	75
F3	100
F4	105
F5	110
F6	56
F7	80
F8	100
F9	110
F10	123
F11	48
F12	78
F13	100
F14	120
F15	148

The folding endurance value of F1 to F15 was found to be 48-110. From the results obtained from the above formulations, all formulations showed folding endurance value complies with in the limit 100-150except F1, F2, F6, F7, F11 and F12 fail to complies with the limit as per previous value.

SURFACE PH OF FILMS: (Birari A.E et al., 2014),

The surface pH of films was determined to investigate the possible side effect because of change in pH in vivo, since an acidic or alkaline pH may cause

irritation to oral mucosa. The film to be tested was placed in a test tube and was moistened with 1.0 ml of distilled water and kept for 30 second. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibrating for 1 min. The average of three determinations for each of the formulation was taken and standard deviation was also calculated. Surface pH of all films was found to be within the limits 6-7.

Table 10: Determination of Surface pH for Different formulations of perindopril films (F1-F15)

FORMULATION	SURFACE pH
F1	6.14±0.05
F2	6.25±0.10
F3	6.35±0.02
F4	6.5±0.08
F5	6.45±0.05
F6	6.65±0.05
F7	6.73±0.05
F8	6.82±0.02
F9	6.75±0.5
F10	6.77±0.06
F11	6.8±0.10
F12	6.7±0.05
F13	6.9±0.07
F14	6.5±0.12
F15	6.85±0.08

DISINTEGRATION TEST (USP 2007)

Disintegration test for all prepared formulations was carried out using disintegration test apparatus as prescribed in USP 2007. F1-F15 showed a

disintegration time of 7-58minutes. From the results obtained, by increasing the concentration of polymer, disintegration time was increased.

Table 11: Determination of disintegration time for different formulations of perindopril films (F1-F15)

Formulation code	Disintegration time (seconds)
F1	7
F2	12
F3	23
F4	28
F5	40
F6	10
F7	12
F8	20
F9	24
F10	35
F11	5
F12	9
F13	15
F14	25
F15	33

The disintegration time of F11 was found to be 5 seconds which took less time as compared to all other formulations (F1-F15). From the results obtained from the above formulations, other thanF5,F10,F15 disintegration time of all films was found to be within the limit as 5-30 seconds as per specification (USP 2007). Based on the disintegration time alone, F11 can be lead to develop perindopril as fast dissolving delivery system.

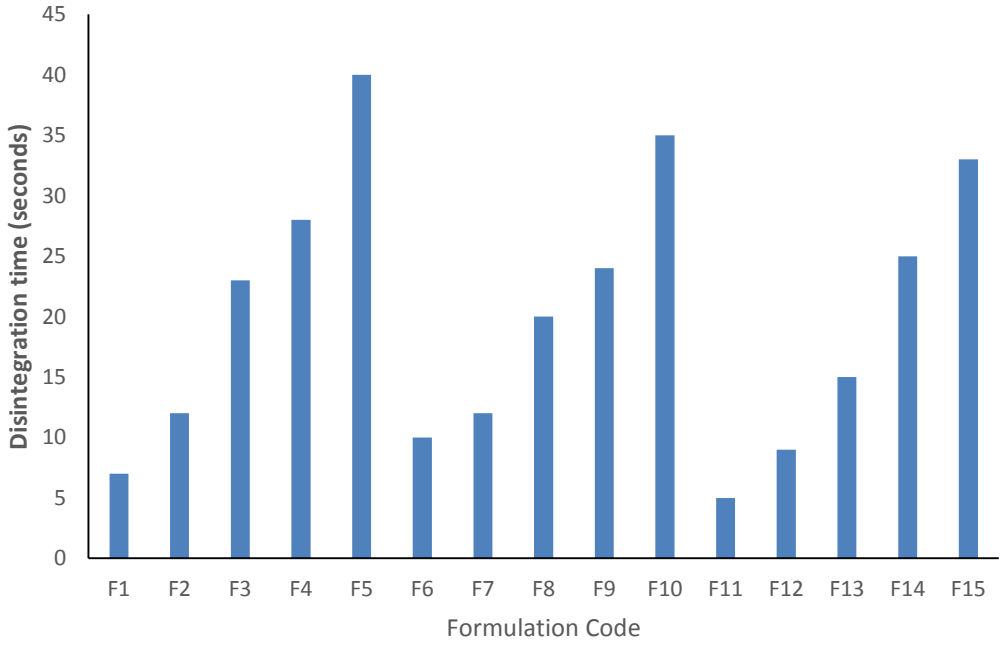


Figure 12: Determination of disintegration timeof different formulations of perindopril fast dissolving films (F1-F15)

DRUG CONTENT UNIFORMITY (Velmurugan S *et al*., 2013)

Percentage of drug content for different formulations was calculated and the results were shown in the table 12.

Table 12: Determination of drug content uniformity for different formulations of perindopril mouth dissolving films (F1-F15)

Formulation code	Drug content (%)
F1	86
F2	90
F3	100
F4	102
F5	104
F6	87
F7	92
F8	99
F9	113
F10	104
F11	85
F12	98
F13	106
F14	97
F15	90

Percentage of drug content of F9 was found to be 113% and was considered as best formulation compared to the other formulation. The formulations showed percentage drug content 85-113%. From the results obtained from the above formulations. The drug content of films should be complies with the limit as 85-110% as per IP specifications (IP 2007).

***Invitro* diffusion studies** (Rahul Nair et al.,2012).

In vitro drug release studies were performed by using Franz diffusion cell with dialysis membrane. It consists of a donor compartment and a receptor compartment. The receptor compartment was filled with 20ml of phosphate buffer solution as a diffusion medium. The prepared film was taken in the receptor compartment the medium was continuously stirred at 50 rpm using magnetic beads and the temperature was maintained at 37±1˚C. 1ml sample of receptor fluid was withdrawn at predetermined intervals and volume was replaced with same volume of 1ml phosphate buffer solution the sample analyzed spectrophotometrically at 210 nm using JASCO V 530.The cumulative amount of drug permitted was calculated and plotted against time.

Table 13: Determination of *in-vitro* diffusion study of different formulations of perindopril fast dissolving film (F1-F5)

Time (minutes)	Cumulative percentage release of perindopril fast dissolving film				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
2	24	22	27	23	22.5
4	39	38	37	42	40
6	44	48	43	46	43
8	50	58	57	57	53
10	64	66	70	69	65
12	78	74	78	78	73
14	82	89	86	82	80
16	87	-	-	89	85

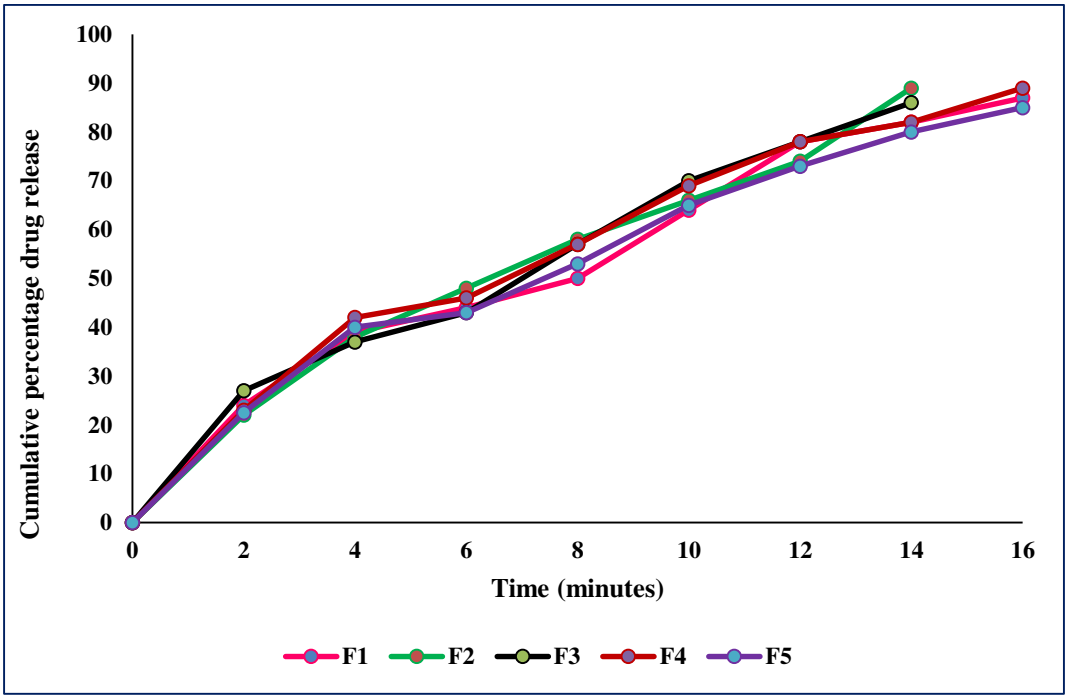


Figure 12: Determination of *in-vitro* release of Different formulations of perindopril fast dissolving film (F1-F5)

Table 14: Determination of *in-vitro* diffusion study of different formulations of perindopril fast dissolving film (F6-F10)

Time (minutes)	Cumulative percentage release of perindopril fast dissolving film				
	F6	F7	F8	F9	F10
0	0	0	0	0	0
2	15	17	20	22	21
4	30	33	38	36	37
6	38	40	43	42	45
8	52	54	58	55	57
10	60	63	67	62	66
12	73	75	78	77	74
14	75	78	84	87	86
16	84	87	89	90	91

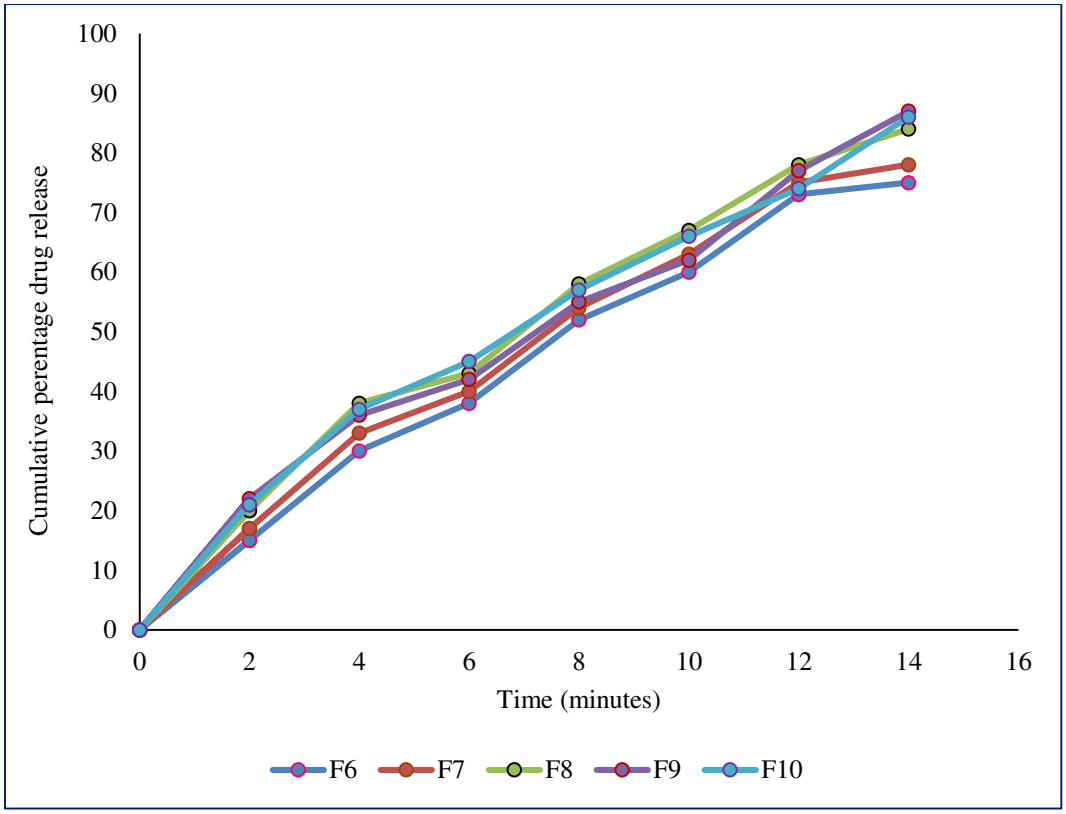


Figure 14: Determination of *in-vitro* release of Different formulations of perindopril fast dissolving film (F6-F10)

Table 15: Determination of *in-vitro* diffusion study of different formulations of perindopril dissolving film (F11-F15)

Time (minutes)	Cumulative percentage release of perindopril fast dissolving films				
	F11	F12	F13	F14	F15
0	0	0	0	0	0
2	17	24	21	36	29
4	33	50	39	64	42
6	41	71	56	82	57
8	59	82	77	91	69
10	68	93	89	93	76
12	79	96	92	96	88.2
14	84	97	95	97	95.7
16	92	-	98	-	-

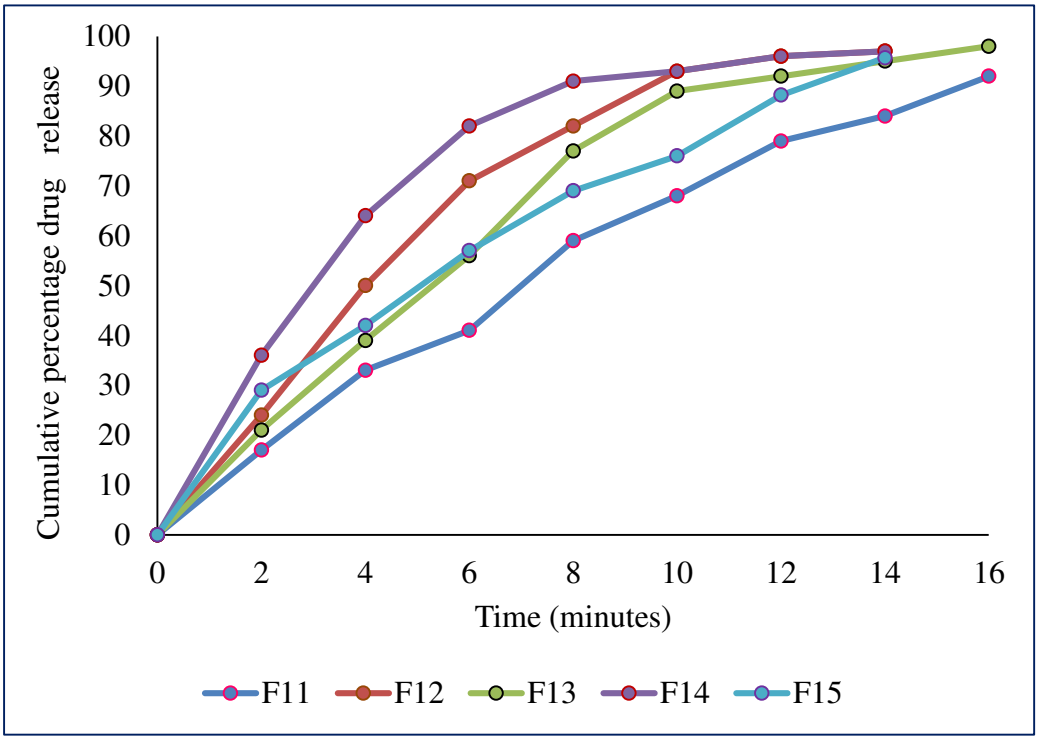


Figure 15: determination of *in-vitro* release of different formulations of perindopril fast dissolving film (F11-F15)

Stability studies of F13 formulation:

Final optimized formulation was subjected to aggravated conditions of temperature and relative humidity by wrapping it in aluminium foil and packaging it in glass container. The films were kept in stability chamber, at 40 ± 20C temperature and 75 ± 5% RH for 3 months. After 3 months the films were tested.

Table 16: Stability Study for Formulation F13

parameter	Initial	3 month
Thickness(mg)	99±2.6	99±3
Weight variation	47±2	48±1.5
Folding endurance	103	105
Disintegration time(sec)	15	16
Percentage drug content (%)	106	107
Surface pH	6.9±0.07	6.9±0.2

Table 17:*Invitro*diffusion study for optimized formulation

Time (minutes)	Initial	After 3 month
0	0	0
2	21	22
4	39	38
6	56	55
8	77	75
10	89	87
12	92	90
14	95	94
16	98	97

The optimized formulation F13 was evaluated for the stability studies which was stored at room temperature (30± 20C);For three months. From the evaluation, it was found that there is no significant change in appearance, pH, folding endurance, surface pH, drug content, *in vitro* disintegration time and percentage drug diffusion study.

Kinetic analysis of *in-vitro* release data

To analyze the *in-vitro* release data, various kinetic models, the zero-order, the first-order, the Higuchi and the Korsmeyer-Peppas models, were used to describe the release kinetics.

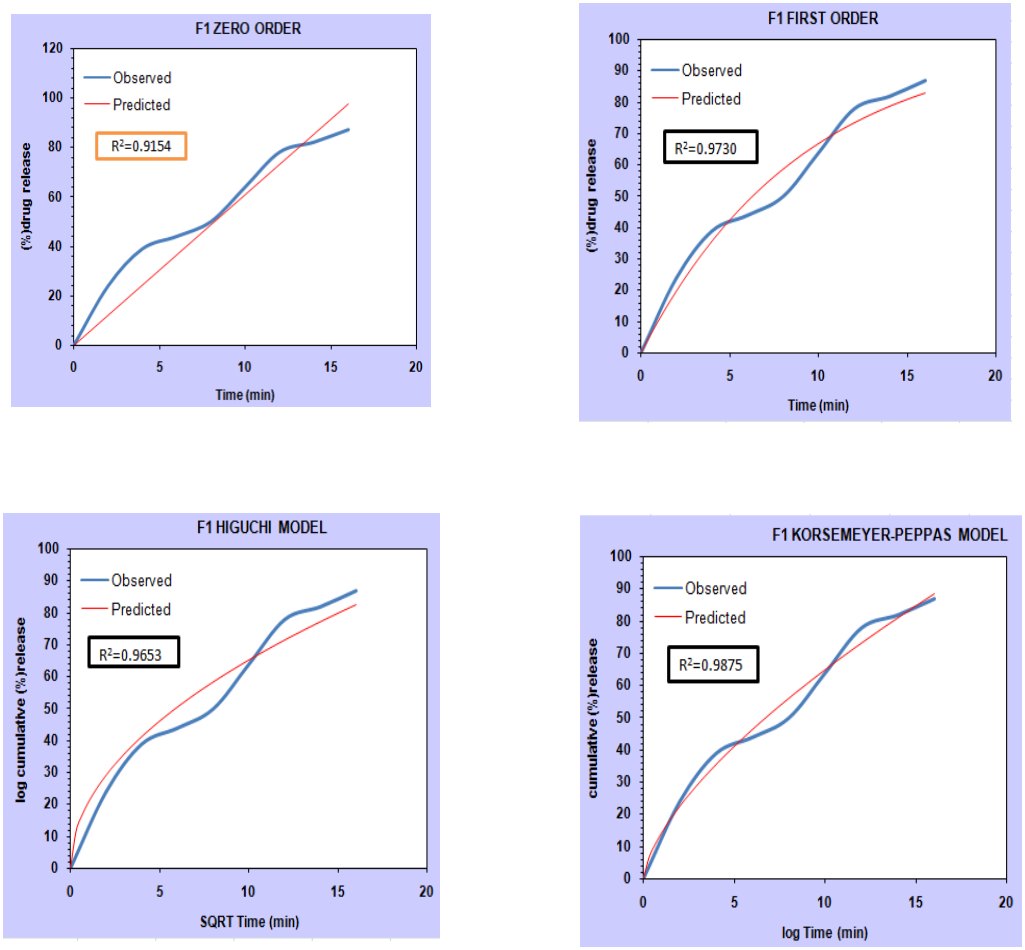


Figure 16: Drug release kinetics of F1

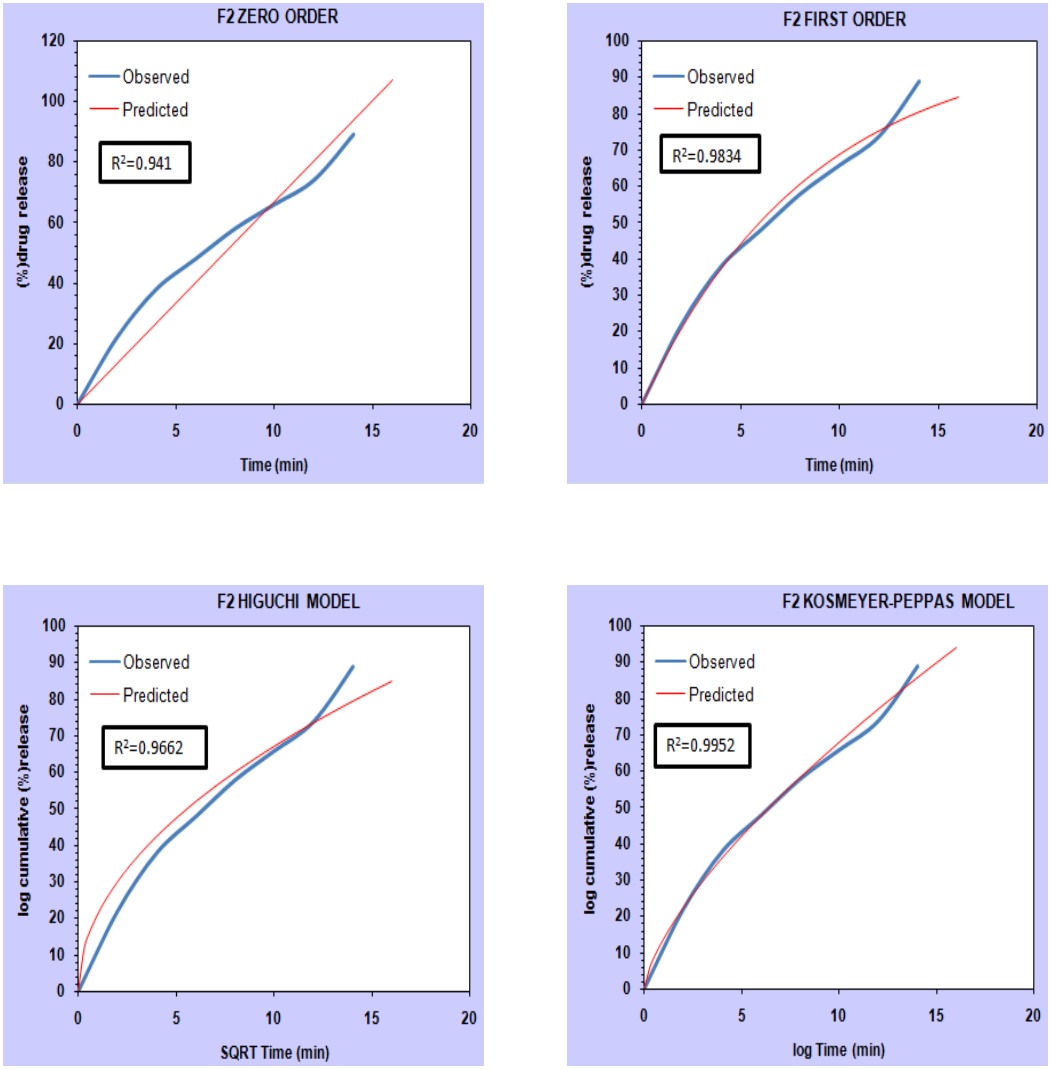


Figure 17: Drugrelease kinetics of F2

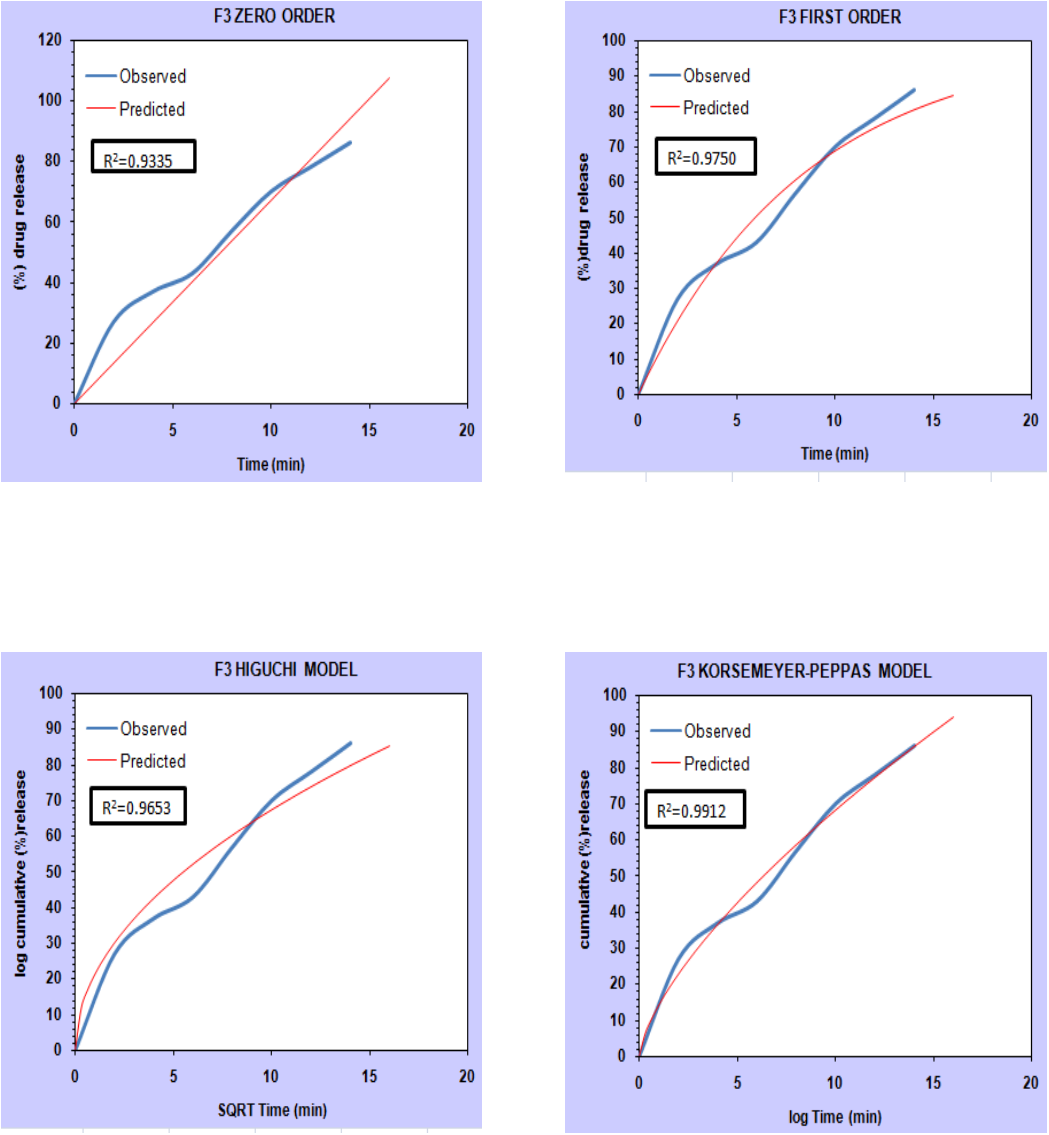


Figure 18: Drug release kinetics of F3

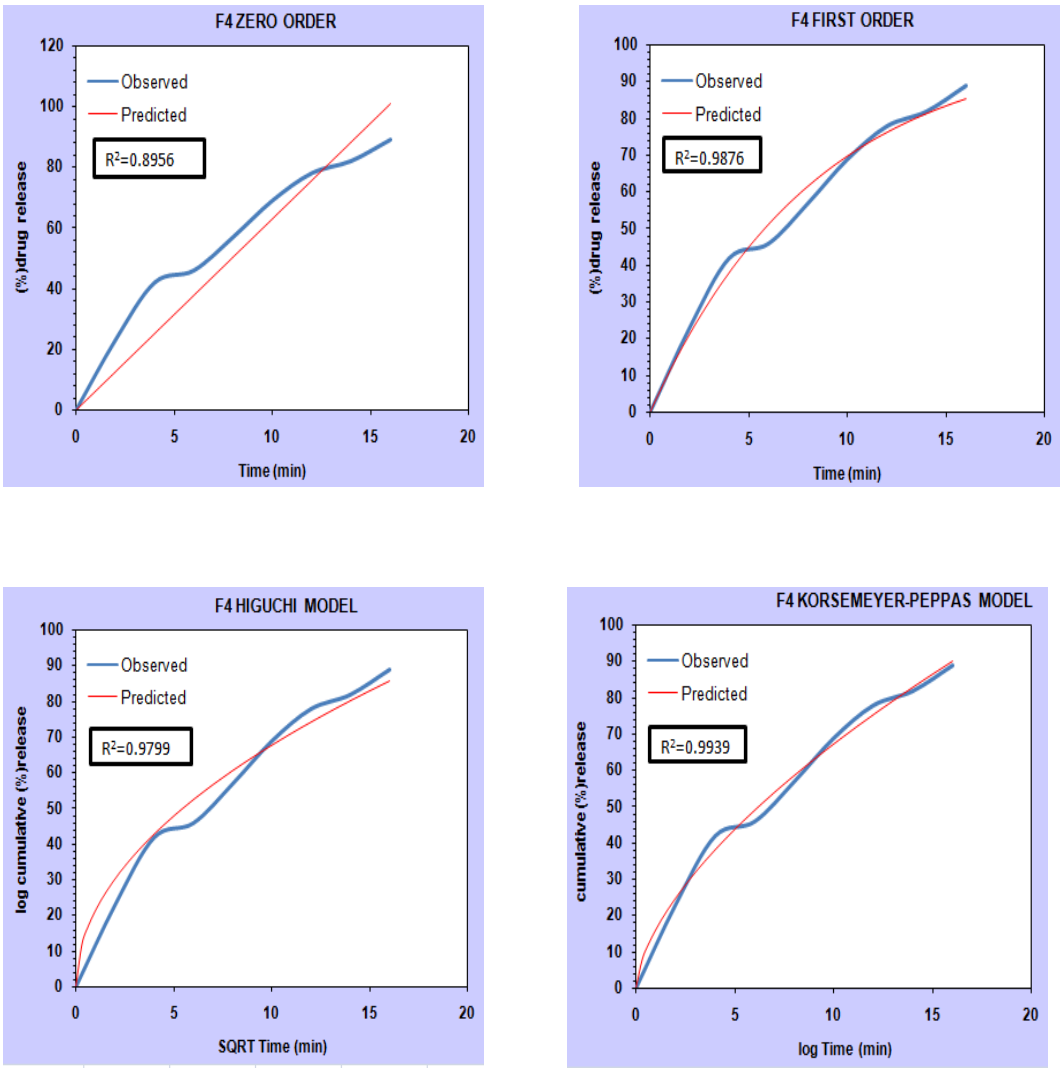


Figure 19:Drug release kinetics of F4

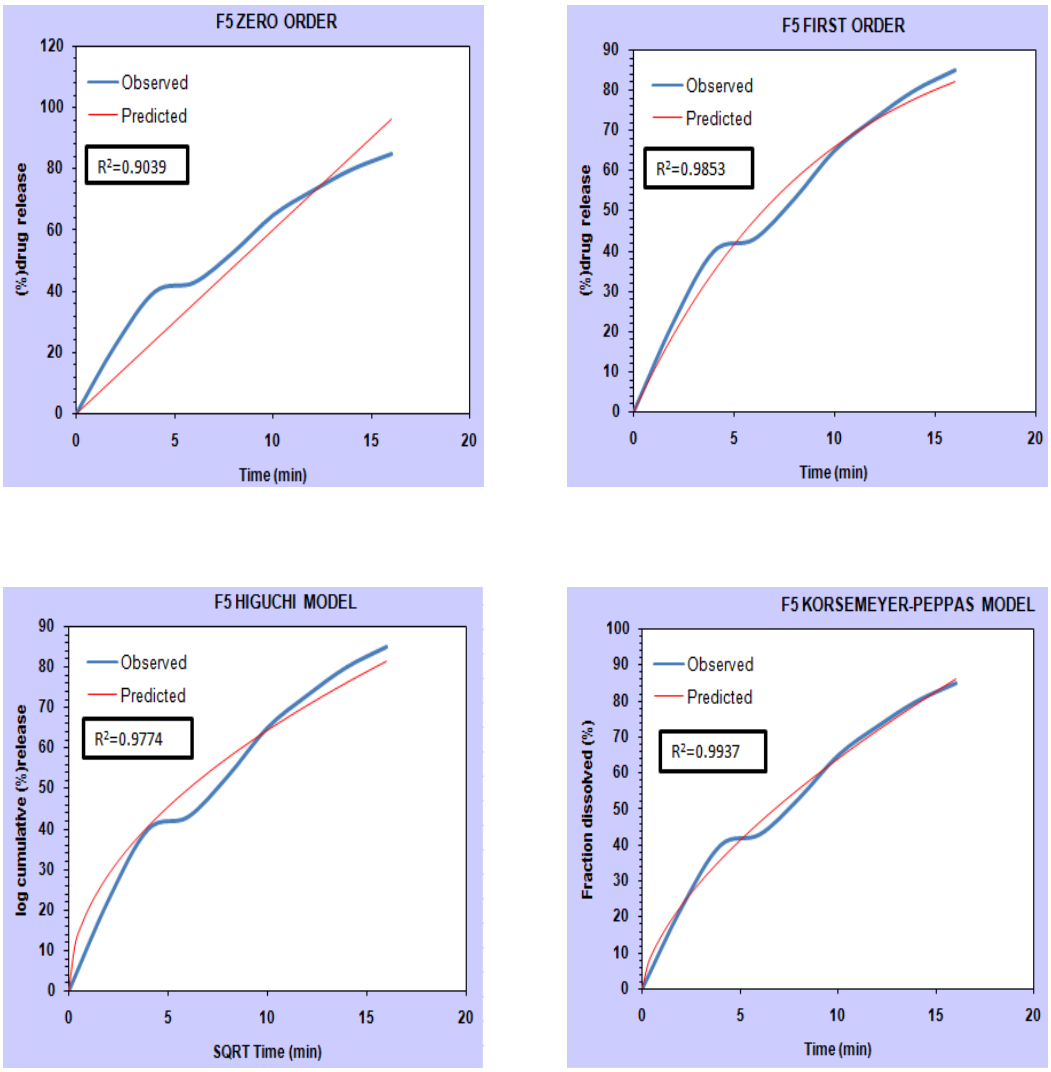


Figure 20: Drug release kinetics of F5

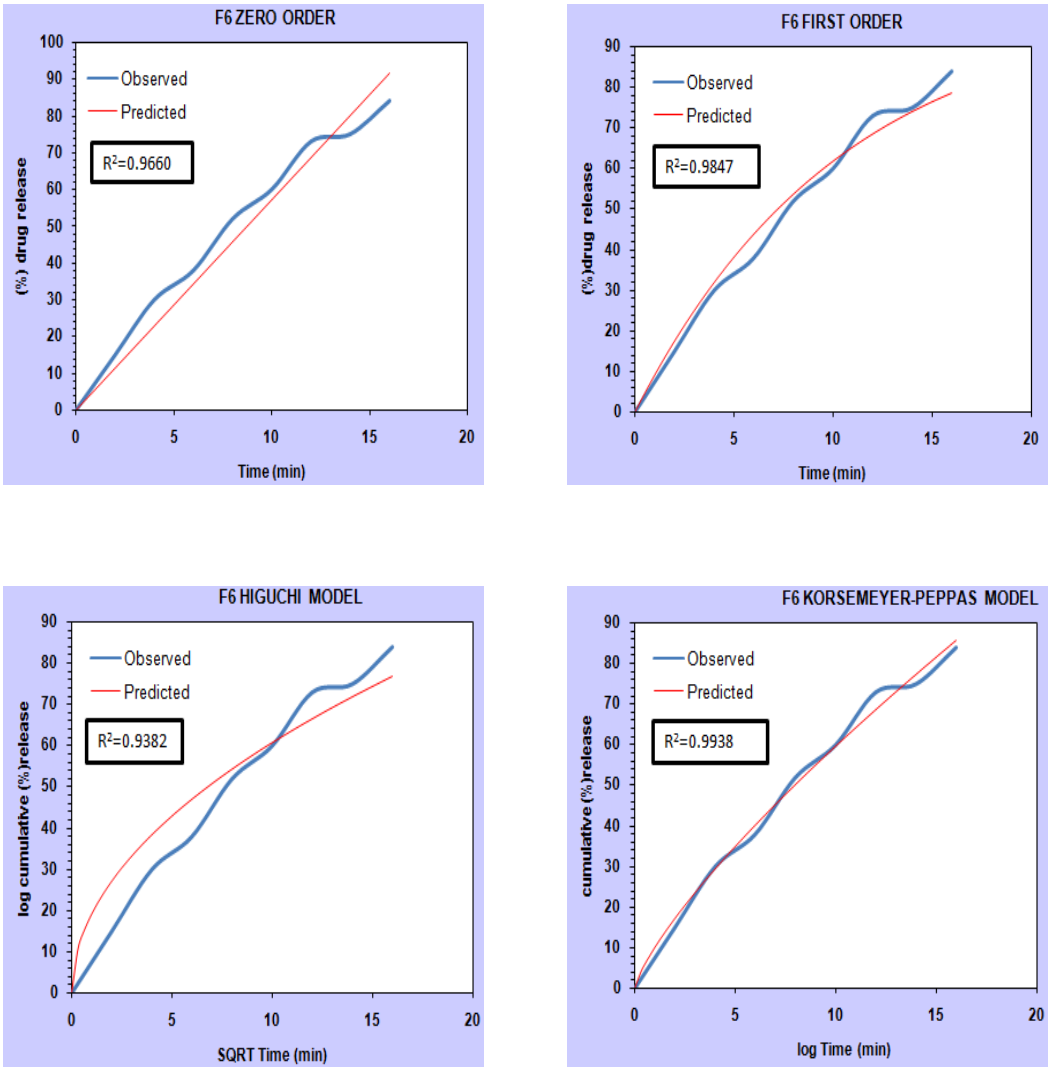


Figure 21:Drug release kinetics of F6

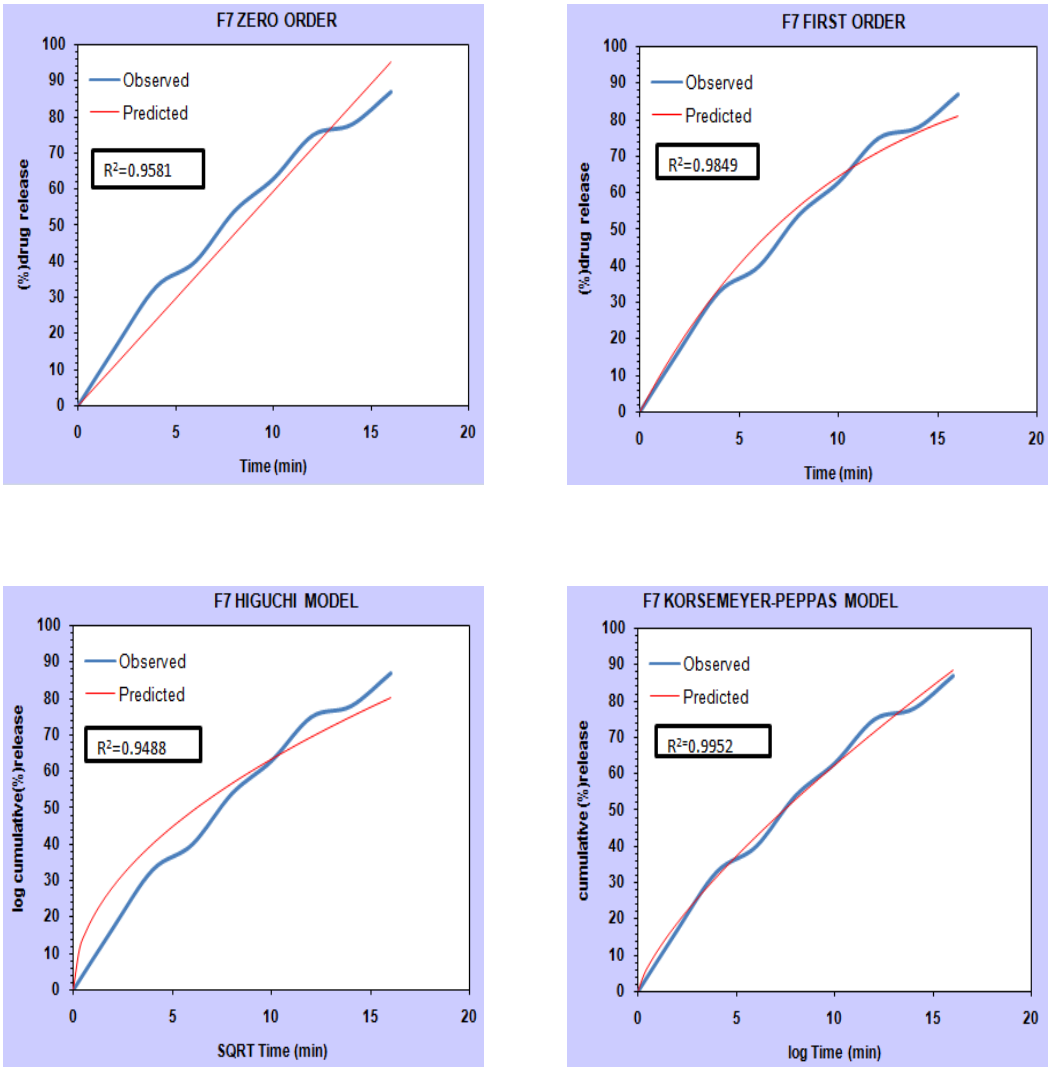


Figure 22:Drug release kinetics of F7

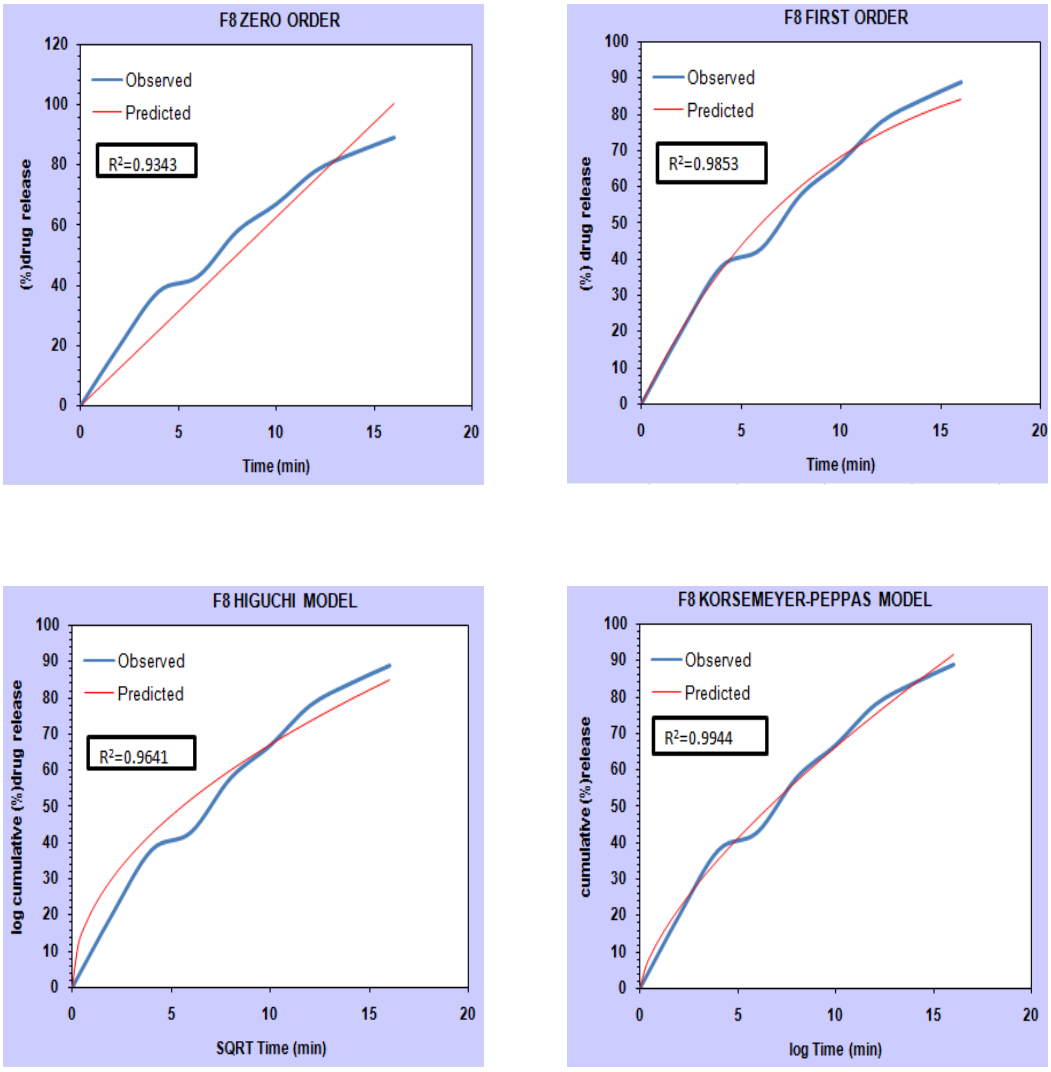


Figure23 :Drug release kinetics of F8

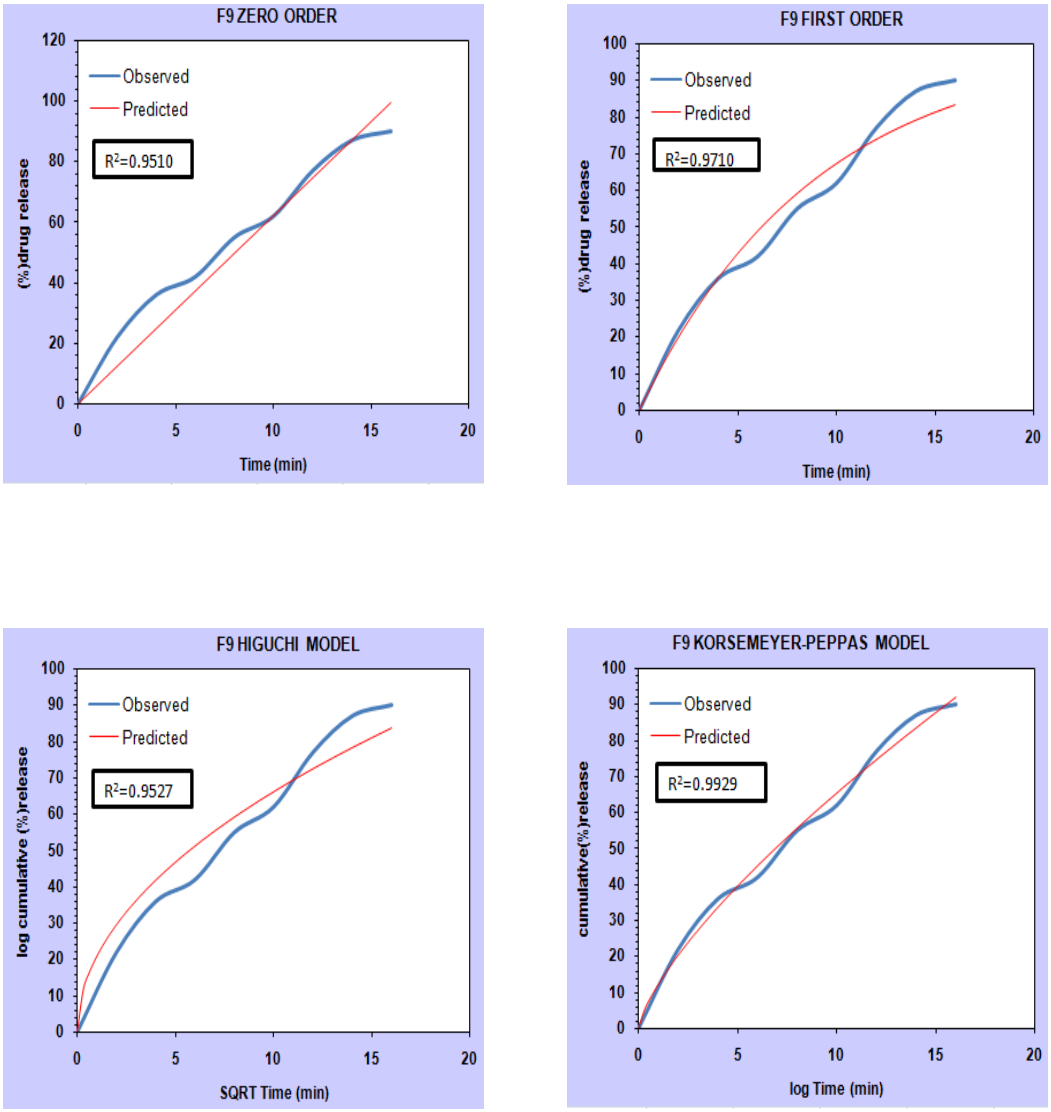


Figure24 :Drug release kinetics of F9

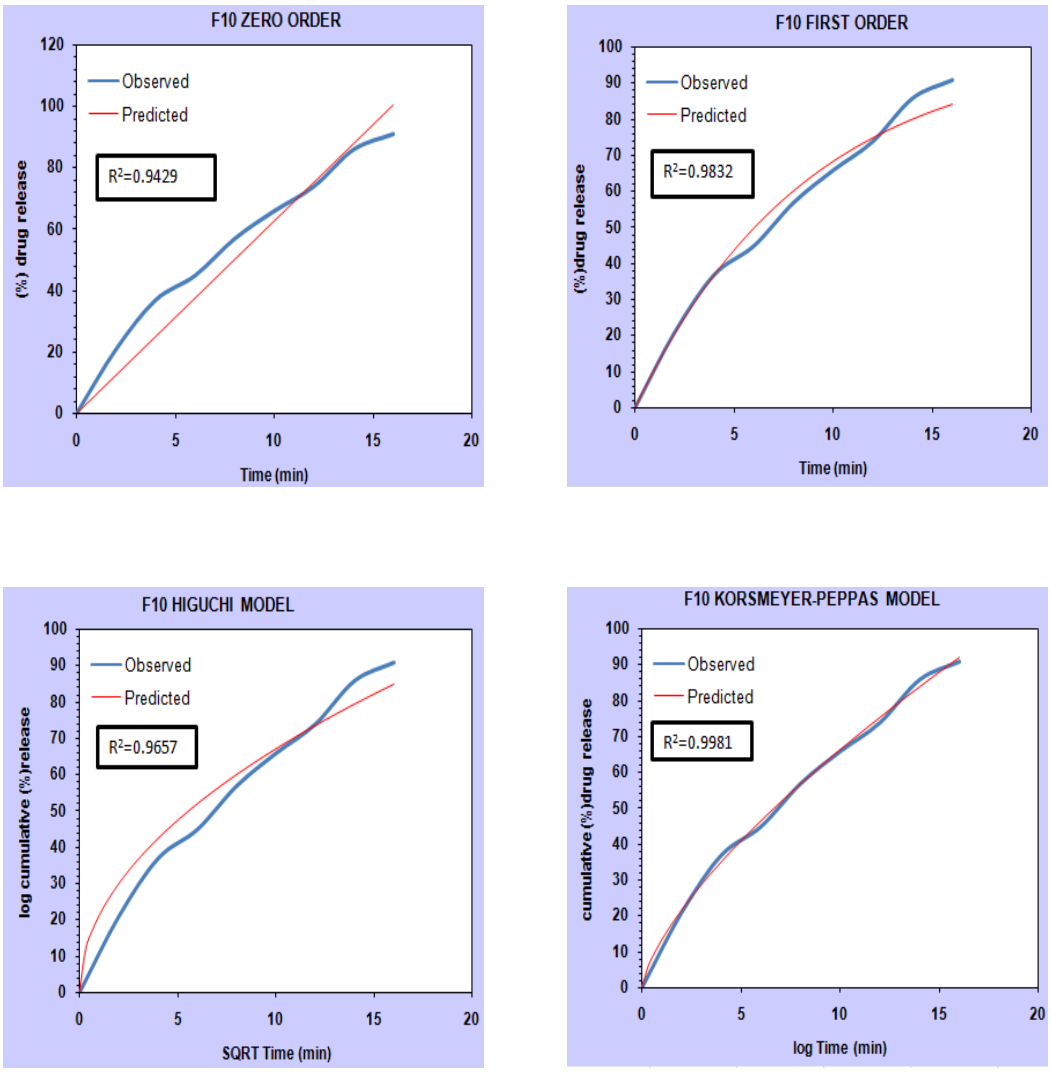


Figure25 :Drug release kinetics of F10

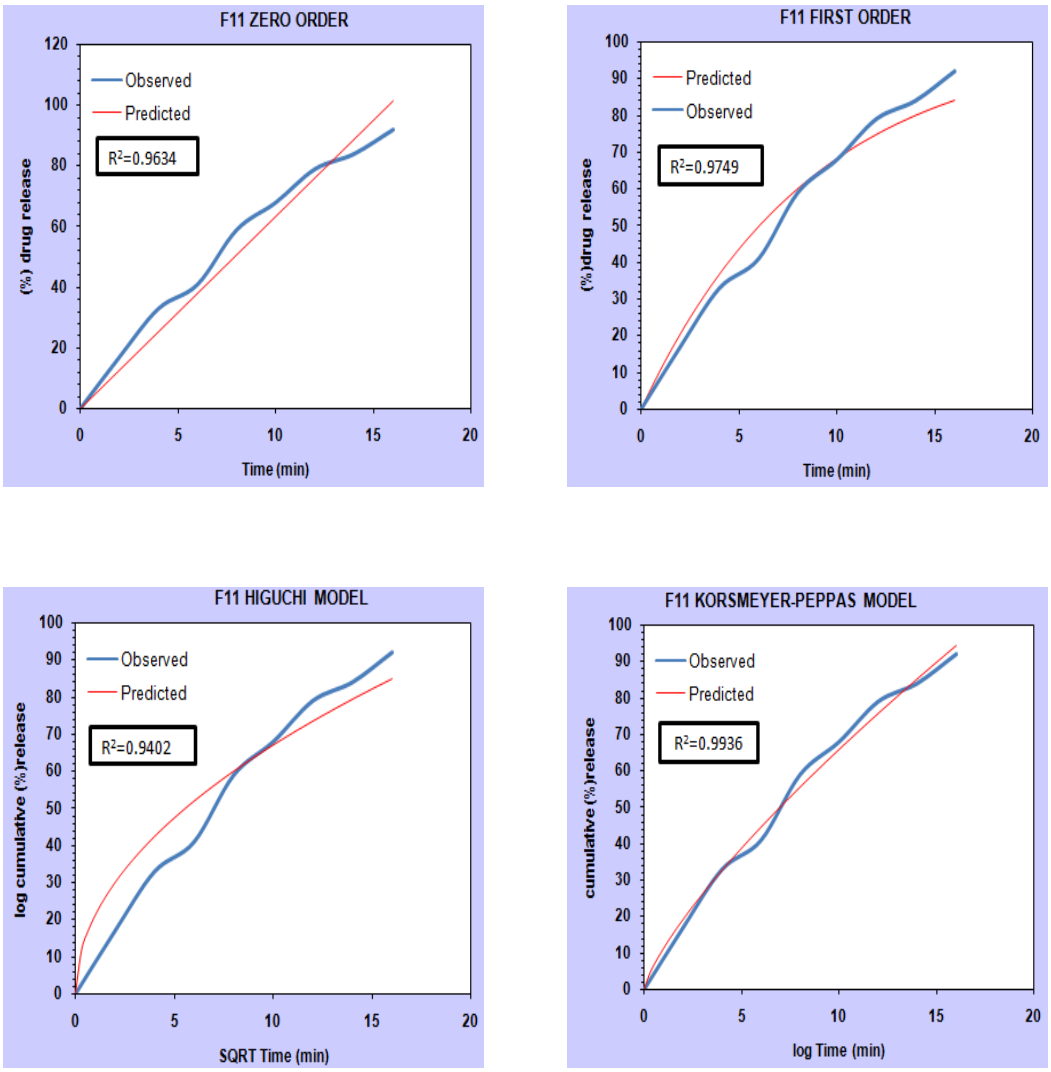


Figure 26:Drug release kinetics of F11

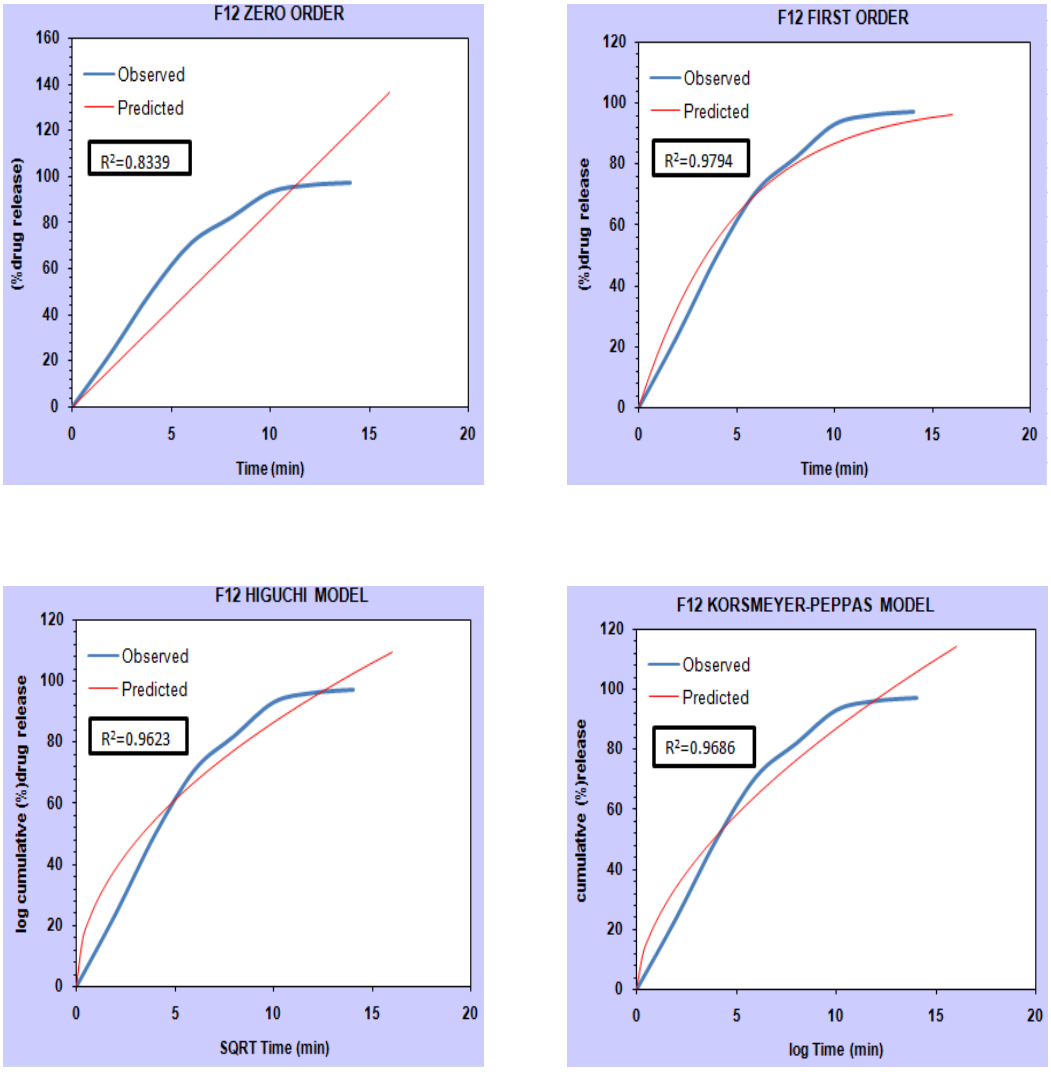


Figure 26:Drug release kinetics of F12

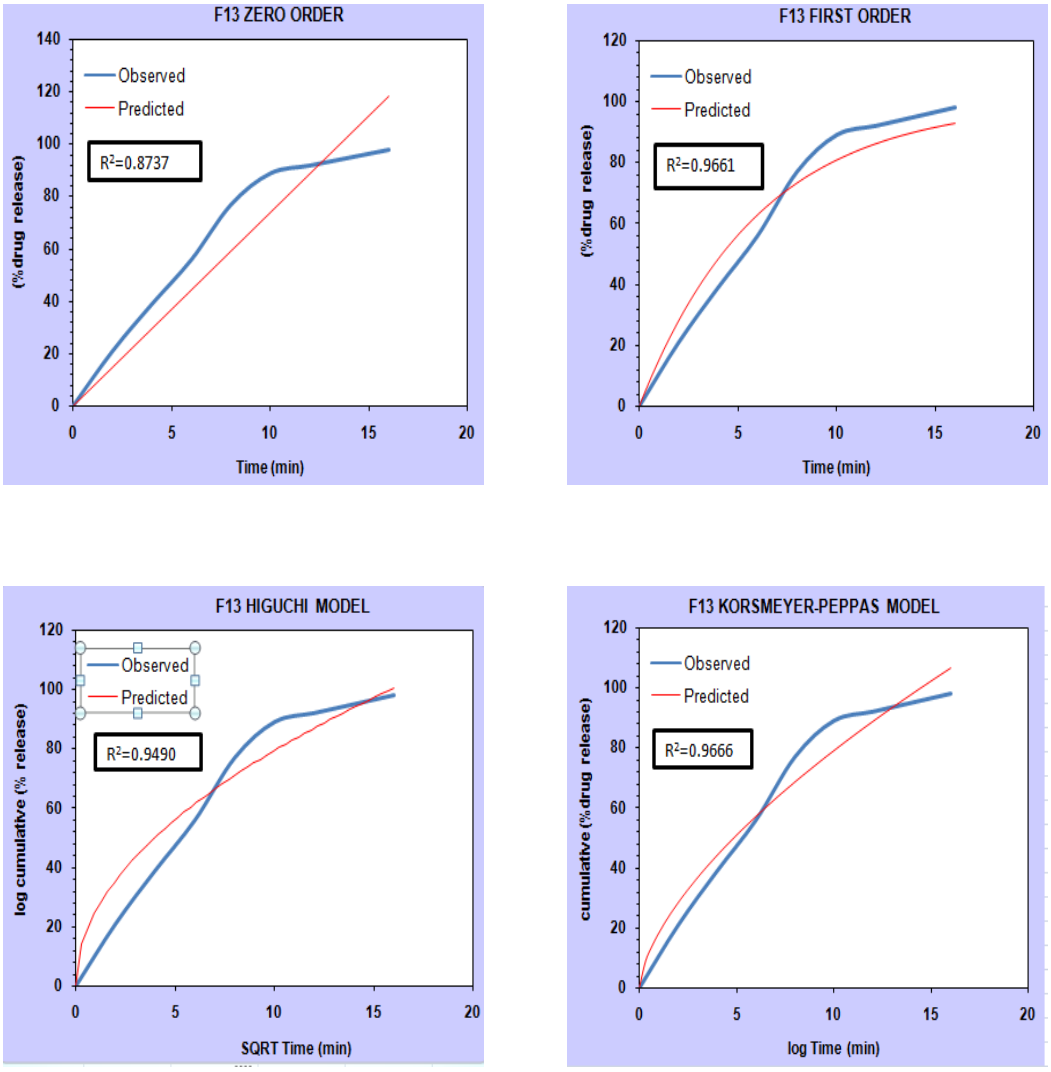


Figure 27:Drug release kinetics of F13

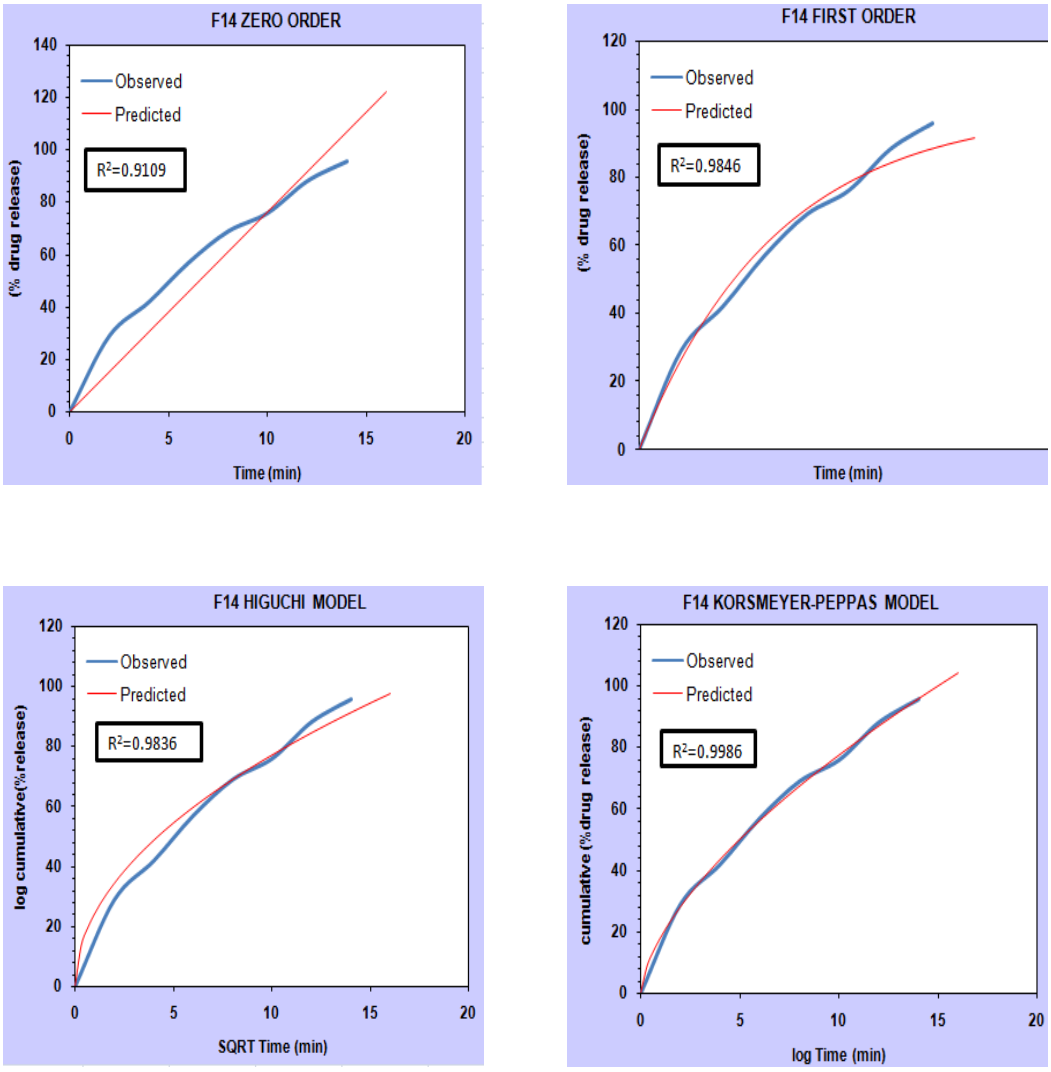


Figure28 :Drug release kinetics of F14

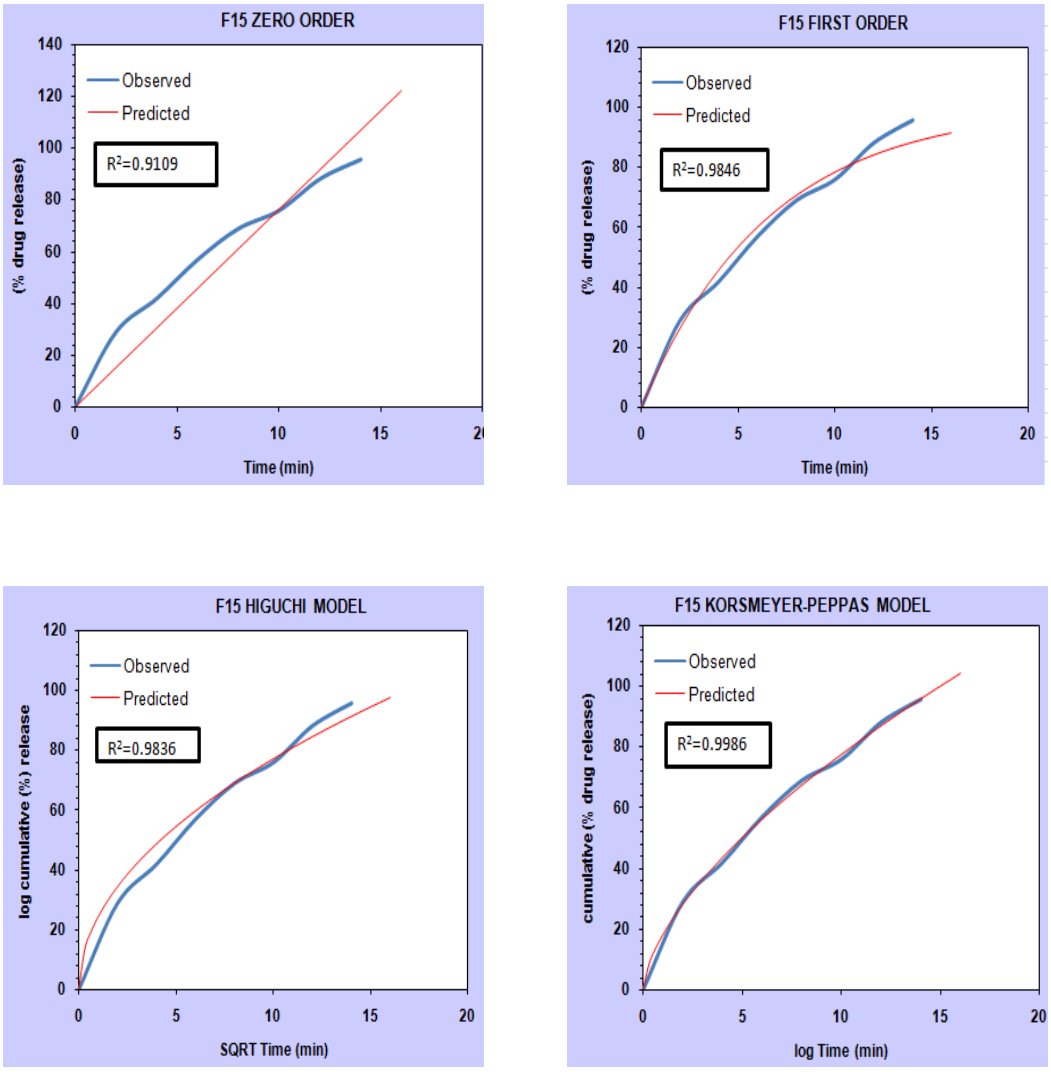


Figure 29:Drug release kinetics of F15

Table 17: Kinetic analysis of *in-vitro* drug release data o formulations F1-F15

Formulation code	Zero order R^2	First order R^2	Higuchi model R^2	Korsemeyer-peppas equation n
F1	0.9154	0.973	0.965	0.658
F2	0.941	0.983	0.966	0.690
F3	0.933	0.975	0.965	0.680
F4	0.8956	0.987	0.979	0.620
F5	0.903	0.985	0.977	0.631
F6	0.966	0.984	0.938	0.771
F7	0.958	0.984	0.948	0.742
F8	0.934	0.985	0.964	0.686
F9	0.951	0.971	0.952	0.725
F10	0.942	0.983	0.965	0.695
F11	0.963	0.974	0.940	0.764
F12	0.833	0.979	0.962	0.578
F13	0.8737	0.966	0.949	0.634
F14	0.9109	0.984	0.983	0.629
F15	0.9109	0.984	0.983	0.629

In order to determine the release model the *in vitro* release data were analyzed according to zero order, first order and diffusion controlled mechanism according to simplified higuchi model. The preference of a certain mechanism was based on the coefficient of determination for the parameters studied, where the highest coefficient of determination is preferred for the selection of the order

of release. However in many experimental situations the mechanism of drug diffusion deviates from the Fickian equation and follows a non-Fickian (anomalous) behavior. In the cases the Korsemeyer-peppas model was used to analyze the release kinetics.Using the Korsemeyer and Peppas model, n = 0.45 indicates case I or Fickian diffusion, 0.45 n> 0.89 indicates anomalous behavior or non-Fickian transport, n = 0.89 indicates case II transport and n greater than 0.89 indicates super case II transport.

Release of all the formulations followed first order kinetics, exhibited diffusion controlled mechanism as indicated from the highest coefficient of determination (r^2). According to the Korsemeyer-peppas model anomalous (non Fickian release) was observed in all formulations as indicated from the release exponent which was in the range of 0.57-0.77 for these formulations.

It was found that the optimized formulation F13 follows first order kinetic model as it had highest R^2 value with Korsemeyer – Peppas mechanism. The "n"exponent value of optimized batch was found to be 0.63. Hence it shows the optimized formulation followed non-Fickian diffusion.

SUMMARY AND CONCLUSION

Perindopril is a hypertension drug. Hypertension is one of the primary risk factors for cardiovascular diseases, including cardiovascular stroke. The absolute bioavailability of perindopril is approximately 60-75%. Following absorption, perindopril is hydrolyzed to Perindoprilat, which has an average bioavailability of 20%. However, food decreases the extent of biotransformation to Perindoprilat and reduces its bioavailability by 35%.To overcome the above mentioned problems an attempt was made to develop and to improve the solubility of drug and reduce side effects, it was attempted to develop fast dissolving films with some natural polymer.

FTIR spectroscopic studies were carried out in order to establish compatibility between drug and carriers. The results were concluded that there were no chemical interactions between drug and the carriers used, so they could be used for the formulation of perindopril fast dissolving films.

DSC studies were carried out for optimized formulation a sharp exothermic peak observed at 127°C corresponding to its melting point of the drug. (126°C -128°C). The results were concluded that there were no chemical interactions between drug and the carriers used.

Around fifteen formulations of perindopril were developed as fast dissolving films using various excipients which were found to be compatible using FTIR of films. Formulation F1-F15 was perindopril fast dissolving films prepared using three different polymers such as sodium alginate, Xanthan gum and pectin.

Perindopril films were evaluated for quality control tests such as thickness, weight variation, folding endurance, SEM, surface pH, disintegration time, *in-vitro* diffusion, drug content, kinetic studies and stability study.

The thickness of all formulations complies with the limit. Weight variation of F15 alone does not complies with the standard. The folding endurance of all formulation with in the limit 100-150 except F1,F2,F6,F7,F11 and F12 fail to complies with the limit as per standard value. Scanning electron micrograph of the optimized formulation F13 are shown at a magnification ratio of X5000 at 20kv. The surface morphology of the prepared nanoparticles was shown .The surface pH of all formulations complies with the limit. The disintegration time of all the formulations except F5, F10 and F15 fails to be within the limit. The drug content of all the formulations was found be within the limit. The *in-vitro* drug study of F13 was found to give the highest % diffusion than other formulation. From the *in-vitro* diffusion studies of fast dissolving films, it was observed that F13 showed more % diffusion at 16 minutes.

The *In vitro* data was fit to kinetic models to explain permeation profiles. The coefficient of correlation of each of the kinetics was calculated and compared. From the Regression coefficient value it was concluded that it follows first order kinetics. The data was further treated as per Higuchi's equation indicated that the drug released by diffusion predominated with the formulation and Korsemeyer peppas model exponent value n describes n (value 0.45-0.85) shows non Fickian iffusion.

Optimized formulation F13 were found to be stable at accelerated stability conditions.

CONCLUSION

Perindopril fast dissolving films have been successfully prepared by solvent casting method.

Perindopril is a anti hypertension drug was selected for the preparation of fast dissolving films.

Xanthan gum, sodium alginate and pectin were used as polymers for the preparation of perindopril mouth dissolving films.

Perindopril films were prepared by solvent casting method using Xanthan gum, sodium alginate, pectin at 100,150,200,250,300 mg respectively.

Based on this physiochemical characterization *in vitro* drug diffusion and drug release kinetics of perindopril showed 93.5% of drug at the end of 16^{th} mins.

The evaluation test for films of perindopril suggest that it is promising to be developed as fast dissolving films with above mentioned excipients which can enhance the diffusion, thereby the release and hence the bioavailability may be effected and may have impact on its bioavailability.

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